iStent®
TRABECULAR
MICRO-BYPASS

PRODUCT
MONOGRAPH

IN CONJUNCTION WITH CATARACT SURGERY,
iSTENT REDUCES INTRAOCULAR PRESSURE (IOP)
BY IMPROVING AQUEOUS HUMOR OUTFLOW
THROUGH THE PHYSIOLOGIC PATHWAY

GLAUKOS®
Changing Perspectives

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I. INTRODUCTION

The following pages provide a detailed overview of open-angle glaucoma (OAG), including landmark clinical trials, treatment options, and the iStent® Trabecular Micro-Bypass Stent. The content within this document has been extrapolated from peer-reviewed publications and data submitted to the FDA for the approval of use of the iStent device.

The iStent Trabecular Micro-Bypass Stent (Models GTS 100R and GTS 100L) represents the first in a new class of devices for the treatment of glaucoma referred to as Micro Invasive Glaucoma Surgical (MIGS) devices. MIGS devices have the following characteristics:

- *CAN BE IMPLANTED THROUGH A MICRO INCISION*

- *ARE IMPLANTED IN AB INTERNO PROCEDURES (IE, WITHOUT INCISING THE CONJUNCTIVA OR SCLERA)*

- *IMPROVE PHYSIOLOGIC OUTFLOW*

The iStent device is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild-to-moderate open-angle glaucoma who are currently treated with ocular hypotensive medication.

All claims and statements are referenced.

II. OVERVIEW OF GLAUCOMA

A. EPIDEMIOLOGY AND COSTS

Glaucoma affects more than 2.6 million people in the United States and is the second leading cause of blindness.[1,2] Open-angle glaucoma (OAG) is the most common form of the disease and is often characterized by ocular hypertension (OHT) combined with optic neuropathy. Ocular hypertension is defined as IOP of ≥21 mm Hg and affects between 3 and 6 million people in the United States.[3] Elevated intraocular pressure is the number one risk factor for disease progression and vision loss.

While risk for disease progression, defined as visual field (VF) loss due to damage to the optic nerve, varies amongst patients, numerous clinical trials have demonstrated that significant fluctuations in high peak IOP may also increase the risk for vision loss.[4,5]

Patient noncompliance with ocular hypotensive medication can result in fluctuating, uncontrolled IOP.[6,7] Recent research has shown that up to 90% of patients in the United States are noncompliant with their ocular hypotensive drug therapies.[7]

Despite the risks associated with noncompliance, prescription medication remains the most common treatment for glaucoma, comprising approximately 50% of the $2.5 billion annually spent on the disease.[8,9] Prescription therapies across the disease are estimated to comprise only about 10% of the US national healthcare expenditure.[10] Thus, the share of the total cost of treating glaucoma accounted for by prescription therapy is approximately 5 times greater than its share of total national healthcare costs.

Evidence of the risks and costs associated with drug therapy, combined with recent advancements in new micro invasive procedures, have resulted in significant proposed changes to the traditional treatment algorithm for OAG. Glaucoma specialists and ophthalmic experts propose earlier intervention with micro-invasive surgical procedures based on patient assessment and clinical goals.

B. DEFINITION OF OAG

Open-angle glaucoma is a chronic, degenerative optic neuropathy characterized by progressive vision loss due to the loss of retinal ganglion cells (RGCs) and optic nerve damage.[11,12] It is generally bilateral, but often asymmetric.[12] The disease is associated with an anterior chamber angle that is open by gonioscopic appearance. There are rare cases in which visual field changes manifest before detectable changes to the optic nerve are seen.

C. RISK FACTORS

Numerous landmark clinical trials have demonstrated that elevated IOP is the number one treatable risk factor for OAG and in preventing disease progression. In addition, a thorough evaluation of epidemiological investigations and clinical trials has determined

the following characteristics as important risk factors for OAG[11,12]:

1. INCREASED IOP
2. OLDER AGE
3. FAMILY HISTORY OF GLAUCOMA
4. AFRICAN ANCESTRY OR LATINO/HISPANIC ETHNICITY
5. THINNER CENTRAL CORNEA
6. LOW OCULAR PERFUSION PRESSURES
7. TYPE 2 DIABETES MELLITUS
8. MYOPIA
9. VARIATION IN IOP

1. INTRAOCULAR PRESSURE

The ciliary body in the eye produces aqueous humor at a relatively constant rate of approximately 2.4 μL/minute during waking hours, and this rate reduces by approximately 45% during sleep.[13] Outflow of aqueous humor occurs via the trabecular meshwork (ie, conventional outflow) and the suprachoroidal space (ie, unconventional or uveoscleral outflow). Elevated IOP does not result from increased aqueous humor production but from reduced aqueous outflow.[11] Research in the physiology of the trabecular meshwork in normal and diseased eyes suggests that the trabecular meshwork is the primary site of aqueous outflow and increased outflow resistance, and thus reduced outflow facility in open-angle glaucoma.[11,12,14-16] Outflow resistance in Schlemm's canal and the trabecular meshwork leaves no other area for pressure release and results in an increase in intraocular pressure. Increased pressure can cause damage to the optic nerve head (ie, cupping), which leads to the brain and the health of which is important for the maintenance of visual function.

Several studies have demonstrated that both the incidence and prevalence of open-angle glaucoma increase as pressure increases within the eye, indicating that IOP plays a key role in the progressive optic neuropathy that is the hallmark of open-angle glaucoma[17-24] (see Figure 1). Normal IOP is generally considered to range between 10 mm Hg and 21 mm Hg. In the Baltimore Eye Survey, the prevalence of OAG was approximately 9 times higher in patients with IOP >21 mm Hg than among those with IOP ≤21 mm Hg.[23] However, IOP cannot be used to diagnose OAG as studies have also demonstrated that a significant proportion of patients diagnosed with OAG have an IOP ≤21 mm Hg, and the vast majority of patients with IOP >21 mm Hg do not have OAG. In addition, there is significant variation between individuals with regard to level of IOP and optic nerve damage.[17,21-23,25-29]

Furthermore, numerous studies have demonstrated that reduction in the level of IOP lessens the risk of visual field progression in OAG.[6,30-34] Specifically, results from the Early Manifest Glaucoma Trial,[34] the Ocular Hypertension Treatment Study,[35] and the Canadian Glaucoma Study[36] indicate that the risk of glaucomatous progression decreased by approximately 10% or more with each 1mm Hg reduction in IOP from baseline.
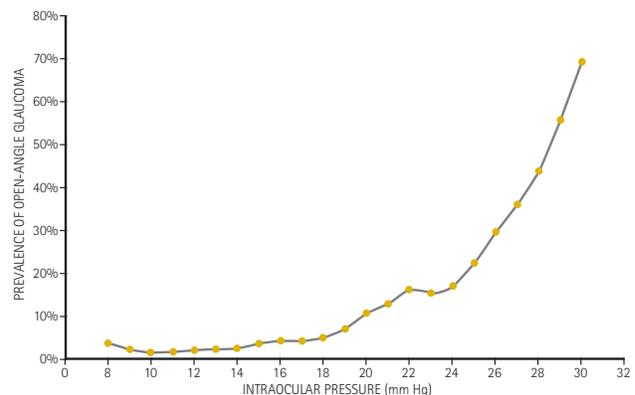
Figure 1. The relationship between prevalence of open-angle glaucoma and intraocular pressure (measured using Goldmann applanation tonometry) in Latinos (n=5970) in the Los Angeles Latino Eye Study.

SOURCE: Adapted with permission from Francis BA, Varma R, Chopra V, Lai MY, Shtir C, Azen SP; for Los Angeles Latino Eye Study Group. Intraocular pressure, central corneal thickness, and prevalence of open-angle glaucoma: the Los Angeles Latino Eye Study. *Am J Ophthalmol.* 2008;146(5):743.

2. AGE

Numerous studies document that age is an important risk factor for OAG.[20-22,25,26] Specifically, among whites, the prevalence of glaucoma among 40-year-olds is between 0.25% and 0.50% but increases to nearly 4% by age 75. Among blacks, prevalence is approximately 2% at age 40 but increases to approximately 10% by age 75.[37]

PREDICTED PREVALENCE OF OAG (95% CI)			
AGE RANGE (Y)	WHITE	BLACK	ASIAN
30–39	–	1.8 (1.2–2.7)	0.4 (0.3–0.6)
40–49	0.4 (0.3–0.6)	2.9 (1.9–4.4)	0.6 (0.4–1.0)
50–59	0.8 (0.5–1.2)	4.6 (3.1–6.8)	1.0 (0.6–1.6)
60–69	1.6 (1.1–2.5)	7.2 (4.9–10.6)	1.6 (1.0–2.4)
70–79	3.3 (2.2–4.9)	11.2 (7.6–16.1)	2.5 (1.6–3.8)
80–89	6.6 (4.4–9.7)	16.9 (11.7–23.8)	3.8 (2.3–5.9)
90–95	10.8 (7.2–15.8)	22.5 (15.7–31.2)	–

Table 1. Estimated Prevalence of Open-Angle Glaucoma According to Age and Race[37]

3. FAMILY HISTORY

Family history appears also to be a risk factor for glaucoma as evidenced by results from the Baltimore Eye Survey, in which the odds of having open-angle glaucoma were approximately twice as high in individuals with a parent, child, or sibling who also had open-angle glaucoma.[38] Similar results were reported in the Los Angeles Latino Eye Study, where the odds were nearly 3 times as high for this same group of patients.[39] Finally, the odds of having OAG were approximately 9 times higher for patients who had a parent or sibling with OAG, according to the Rotterdam Eye Study.[40]

4. ETHNICITY

Ethnicity is clearly an important risk factor for OAG. The prevalence of OAG is higher in individuals of West African, Afro-Caribbean, or Latino/Hispanic origin than of other groups.[20,22,26,28,41,42] African Americans aged 73 to 74 years and ≥75 years had a prevalence of 5.7% and 23.2%, respectively. Similarly, the prevalence of OAG was 3.4% for white individuals aged 73 and 74 years and 9.4% for those ≥75 years.[43]

5. CENTRAL CORNEAL THICKNESS

Applanation tonometry is the standard of care with regard to the measurement of IOP in the physician's office. With applanation tonometry, IOP readings are determined by corneal resistance and stiffness. Consequently, studies have indicated that differences in central corneal thickness (CCT) may affect the accuracy of IOP measurement.[32,44-51] In addition, there are significant differences in corneal thickness between Caucasian Americans, Latinos, and African Americans.[45,52] IOP may be underestimated in those with thinner CCT and overestimated in those with thicker CCT, and no method for correcting for these disparities has been fully validated.[53,54]

In addition, a thinner central cornea may be a risk factor for OAG that is independent of IOP.[55-58]

6. LOW OCULAR PERFUSION PRESSURE

Ocular perfusion pressure is expressed as the difference between the arterial blood pressure and IOP, and is considered a substitute for the venous pressure.[59] There is some evidence that diastolic perfusion pressure <50 mm Hg is associated with a higher prevalence of OAG.[22,60-62] Also, in the Early Manifest Glaucoma Treatment Study, systolic perfusion pressure ≤125 mm Hg was associated with a higher risk of glaucoma progression.[63]

7. TYPE 2 DIABETES MELLITUS

A number of large studies have demonstrated an association between type 2 diabetes mellitus and OAG.[64-68] A prospective cohort analysis of over 76,000 women found that after controlling for age, race, hypertension, body mass index, physical

activity, alcohol intake, smoking, and family history of glaucoma, type 2 diabetes mellitus was positively associated with OAG (RR=1.82), however the association did not strengthen with longer duration of diabetes. Other population-based assessments of Hispanics[65] and non-Hispanic whites[66,67] have also found that patients with type 2 diabetes mellitus are more likely to have OAG.

8. MYOPIA

Large cross-sectional epidemiologic studies in Afro-Caribbeans, Hispanics, non-Hispanic whites, Chinese, Asian Indians, and Japanese suggest that persons with myopia have a higher prevalence of OAG than those without myopia.[29,69-75]

9. VARIATION IN IOP

Although there is some conflicting evidence, there are a number of publications that support IOP fluctuation and variation as an independent risk factor in the progression of OAG. Selected studies have found that patients who exhibited IOP peaks with home tonometry higher than at the office had a 3-times-greater probability of developing visual field loss versus patients who did not experience these types of peaks.[76] A trend analysis in patients diagnosed with OAG found that the long-term standard deviation and range of IOP measurements both correlated with the rate of glaucomatous visual field loss.[77] In a prospective, randomized controlled trial comparing laser trabeculoplasty to medication, visual field decay showed greater correlation to IOP variation (both range and peak) and mean IOP than baseline IOP or degree of IOP reduction.[78] In another prospective home tonometry study, the authors found that eyes with greater variation in IOP were strongly associated with increased progression of glaucoma even after adjusting for office IOP, age, race, gender, and visual field damage at baseline.[79]

D. STAGES OF OAG

There is no universally accepted method for staging the progression of OAG, and a number of staging systems have been published. However, severity of disease is generally categorized by visual field loss due to optic nerve damage. Most staging systems categorize OAG patients into mild, moderate, and advanced/severe categories as follows[80]:

1. MILD: Optic nerve and/or retinal nerve fiber abnormalities, which are consistent with glaucoma and no reproducible visual field loss on standard automated perimetry tests

2. MODERATE: Optic nerve and/or retinal nerve fiber abnormalities, which are consistent with glaucoma and moderate visual field loss that is not within 5° of fixation

3. ADVANCED/SEVERE: Optic nerve and/or retinal nerve fiber abnormalities, which are consistent with glaucoma and significant visual field loss that is within 5° of fixation

III. LANDMARK CLINICAL TRIALS

Numerous prospective, randomized, controlled multicenter clinical trials in both OAG and ocular hypertension with no signs of glaucomatous damage have demonstrated that lowering of IOP is associated with delaying progressive glaucomatous damage to the optic nerve. Four of these are considered landmark trials and are reviewed here: Early Manifest Glaucoma Trial (EMGT), Ocular Hypertension Treatment Study (OHTS), Collaborative Initial Glaucoma Treatment Study (CIGTS), and Advanced Glaucoma Intervention Study (AGIS). However, these studies also demonstrated the limited effectiveness of current treatments.

A. EARLY MANIFEST GLAUCOMA TRIAL (EMGT)

The EMGT was a randomized controlled trial of argon laser trabeculoplasty (ALT) and topical β-blocker vs observation with treatment only if the disease progressed in recruited newly diagnosed (ie, therapy-naïve) patients.[33] Results showed that treatment significantly delayed progression, but glaucomatous damage progressed in nearly half of the patients in the treatment group over the 6-year study period. Lowering IOP with medical therapy and trabeculoplasty (-25%) slowed progression of optical disc and visual field damage. However, nearly half of the patients in the treatment group had progression in glaucomatous damage. The rate of progression in the treatment group was >70% of that in the control group. The EMGT demonstrated that every 1-mm Hg decrease in IOP equates to a 10% reduction in the risk of glaucoma progression.[34]

B. OCULAR HYPERTENSION TREATMENT STUDY (OHTS)

The OHTS sought to evaluate the effect of intervention with medical therapy on patients with ocular hypertension but no signs of glaucomatous damage. Subjects were enrolled and randomly assigned to either treatment with medications or observation. The study objective was to determine if antiglaucoma medications could prevent or delay progression from ocular hypertension to glaucoma.

Visual field abnormalities or optic disc deterioration attributed to primary open-angle glaucoma were seen in 4.4% of treated eyes and 9.5% in untreated eyes ($P<.0001$). For the subset of African American eyes, the incidence of glaucomatous damage was 8.4% in treated eyes versus 16.1% in untreated eyes ($P=.02$). Intraocular pressure declined by 22.5% in the treated group and 4.0% in the untreated group.

However, medical therapy did not prevent all cases of OHT from progressing to glaucoma, as the rate of progression among treated eyes was nearly half that of the rate among untreated eyes.[35]

C. COLLABORATIVE INITIAL GLAUCOMA TREATMENT STUDY (CIGTS)

The CIGTS was a randomized controlled trial of initial treatment of patients with newly diagnosed open-angle glaucoma with trabeculectomy vs pharmacotherapy.[81-86] Lowering IOP with initial filtering surgery (-46%) was as effective as medical therapy (-38%) to inhibit progression of visual field damage, though the amount of reduction was slightly greater after surgery. No significant differences in visual field loss over time were found up to 8 years of follow-up, but approximately 20% of patients in both groups had significant visual field loss by the 8-year follow-up visit. Surgery prevented or delayed glaucomatous progression as measured by optic disc criteria in patients with early open-angle glaucoma.

D. ADVANCED GLAUCOMA INTERVENTION STUDY (AGIS)

The AGIS compared 2 sequences of surgical treatments: 1) ALT, followed by trabeculectomy if ALT failed, and by a second trabeculectomy if the first trabeculectomy failed (ATT group) vs 2) trabeculectomy, followed by ALT if the trabeculectomy failed, and by a second trabeculectomy if the ALT failed (TAT group).[6,87] Higher initial IOP was associated with worse outcomes than lower initial IOP, with the outcomes being worse at 7 years compared to 2 years. These results confirm that low IOP is protective with respect to visual field deterioration.

Surgical outcome varied by race; patients with African ancestry did better with laser trabeculoplasty as first surgery (-30% IOP), while in the longer term (4+ years), white American patients did better with trabeculectomy as first surgery (-48%). The lowest IOP group during follow-up after surgical interventions (-47%) prevented further visual field deterioration in advanced glaucoma patients.[6,87]

A subanalysis of patients demonstrated that increasing age and fluctuating IOP increased the risk for visual field defect progression.[5] In 2008, an analysis of patients enrolled in AGIS indicated that there is a strong correlation between fluctuating IOP and progressive visual field loss, particularly in patients with lower IOP.[88]

IV. TREATMENT OF OPEN-ANGLE GLAUCOMA

A. OVERVIEW AND OBJECTIVES

Glaucoma is a progressive disease that may lead to irreversible ganglion cell damage, resulting in vision loss and potential blindness. The objective of glaucoma management is to provide a significant and sustained decrease in IOP that minimizes the risk of progression (ie, visual field loss) and impact on the patient's quality of life.

Numerous landmark clinical trials have demonstrated that reducing elevated IOP is the most effective means of treating OAG and in preventing disease progression. The primary cause of elevated IOP is an abnormality of the trabecular meshwork, which is lined with endothelial cells to facilitate outflow of aqueous humor from the eye. Injury or death of endothelial cells reduces the ability of the trabecular meshwork to facilitate outflow, causing an increase in fluid backup and IOP.[11,12] Elevated IOP puts pressure on the optic nerve, thereby thinning the neuroretinal rim and enlarging the optic nerve cup. Optic nerve cupping causes the loss of retinal ganglion cells, glia, and supporting vasculature leading to disc changes or disc and progressive visual field loss.[35] While the majority of patients with OAG present with elevated IOP, a substantial minority may not have elevated IOP measurements.[11,12]

Increased IOP has been shown to damage retinal cells,[89] and an increase in pressure of 1 mm Hg is associated with an increased risk of glaucomatous visual field loss of at least 10%.[34-36] Consequently, IOP is a validated surrogate marker for potential visual loss.[33] In addition, elevated IOP is the only modifiable risk factor associated with open-angle glaucoma. Beyond a sustained decrease in IOP, ideal treatments for glaucoma would also ensure patient compliance and possess favorable safety profiles.

Because OAG is a chronic and often asymptomatic condition, preventing disease progression is a challenge for both the patient and the doctor. Determining the probability of successful patient management and prevention of disease progression should be based on the diagnosis, severity of disease, prognosis, management plan, and likelihood of the patient complying with long-term therapy.[80] For example, noncompliance with drug therapy can have a significant negative effect on clinical outcomes. Factors such as patient's quality of life, effects of treatment, life expectancy, lifestyle, costs, and coexisting conditions should all be considered when selecting an initial or additional treatment.[90-94]

B. TREATMENT OPTIONS

The physician managing a patient diagnosed with OAG will select a treatment that is likely to achieve

a target IOP below which there is not likely to be any further damage to the optic nerve. Prior to the introduction of Micro Invasive Glaucoma Surgery implants such as the iStent Trabecular Micro-Bypass stent, treatment options included medical therapy, laser trabeculoplasty, incisional glaucoma procedures, and cyclodestructive surgery. As the least invasive treatment option, medical therapy in the form of topical hypotensive eye drops is typically used as initial therapy. Laser trabeculoplasty is generally the next option for patients who are no longer controlled on medical therapy or are unable to comply with medical therapy due to side effects, cost, or difficulty instilling drops.

Incisional glaucoma surgery and cyclodestructive surgery are typically reserved for patients with severe or advanced disease. While these procedures can produce significant reductions in IOP, they are associated with a relatively high incidence of complications, including complications that are considered serious adverse events.

The choice of initial therapy depends on numerous considerations, and discussion of treatment with the patient should include the relative risks and benefits of these options.

The current economic climate, an increasingly aging population, and heightened patient awareness have elevated the need for personalized patient care in the United States. In the management of OAG, personalized care includes a discussion between the patient and healthcare provider to evaluate options based on medical treatment and patient lifestyle factors. Medical treatment factors include costs of therapy, office visits, side effects, drug interactions, surgical risks, and dosing schedules. Patient lifestyle factors include income, healthcare coverage, busy schedule, forgetfulness, coexisting conditions, and *willingness* to tolerate presenting side effects such as hyperemia or ocular stinging.

C. MEDICATIONS

1. INTRODUCTION

For the majority of patients, medications are used as first-line therapy in open-angle glaucoma. Many studies have been published documenting the efficacy of topical hypotensive

	β–BLOCKERS	CARBONIC ANHYDRASE INHIBITORS	ALPHA AGONISTS	PROSTAGLANDINS AND PROSTAMIDES
MECHANISM OF ACTION	• Decrease aqueous humor production	• Decrease aqueous humor production	• Decrease aqueous humor production and increase uveoscleral outflow	• Increase aqueous humor outflow
OCULAR ADVERSE EFFECTS	• Allergy • Irritation • Burning • Blurring • Keratitis	• Irritation • Induced myopia • Blurring • Keratitis • Conjunctivitis • Dermatitis	• Allergy • Irritation • Conjunctival hyperemia • Dryness	• Increased iris and lash pigmentation • Hypertrichosis • Conjunctival hyperemia • Blepharitis
SYSTEMIC ADVERSE EFFECTS	• Bradycardia • Heart block • Bronchospasm • Decreased libido • Central nervous system depression	• Headache • Nausea • Fatigue • Bitter taste	• Hypertension • Tachycardia • Dizziness • Depression	• Influenza-like symptoms • Joint and muscle pain • Hypertension • Headache
CONTRAINDICATIONS	• Asthma • Obstructive pulmonary disease • Sinus bradycardia • Heart block or cardiac failure	• Severe renal disease	• Narrow anterior chamber angle • Aphakia • Pediatric age • Use of monoamine oxidase (MAO) inhibitors or antidepressant	• History or risk of cystoid macular edema or uveitis

Table 2. Medical therapy risk: Side effects and contraindications.[95]

drugs in lowering intraocular pressure. Compared to other classes of drugs, the side effects associated with medical therapy are relatively benign. However, open-angle glaucoma works insidiously, painlessly, and slowly in causing blindness. Medical therapy is a lifelong process, and success in stopping or delaying glaucomatous progression is dependent on the patient's adherence with the recommended treatment regimen, as well as persistence in maintaining a supply of the drug on hand. Ensuring that patients adhere to their schedules and persist with medical therapy is particularly challenging with patients diagnosed with open-angle glaucoma as the disease is typically symptom-free and loss of vision frequently goes unnoticed. Consequently, there are numerous reports in the literature documenting poor adherence and persistence. Given that consistent lowering of intraocular pressure is the only intervention that has been clinically proven to slow optic nerve damage and visual field loss progression, lack of adherence and persistence are significant clinical concerns. This issue alone raises questions about the use of medical therapy as the sole first-line approach to open-angle glaucoma therapy.

2. NONCOMPLIANCE

Noncompliance is generally considered to be the greatest drawback to medical therapy. Reports of chronic glaucoma patients failing to comply with medical advice began appearing in the literature in the 1970s. In one of the first reports, Bloch et al reported in 1977 on interviews with 40 chronic open-angle glaucoma patients in which 11 patients (27.5%) admitted that they did not take their medication as directed more than once in the previous week.[96]

The patient interview method, however, may underestimate the level of patient noncompliance. Kass et al used an unobtrusive eye drop medication monitor to measure compliance with topical pilocarpine treatment in a sample of 184 patients. Patients in the study administered a mean of 76%

of the prescribed pilocarpine doses, with 21% of patients taking less than one-half of the doses recommend by their physician. When subjects were interviewed, however, they reported taking 97.1% of the prescribed pilocarpine doses. In addition, the rate of compliance was significantly higher ($P<.0001$) in the 24-hour period preceding the return appointment than in the entire observation period.[97]

An additional method of circumventing any bias associated with patient self-reporting is retrospective review of data from large population-based samples. Gurwitz et al derived a study cohort of 2440 patients ≥65 years of age who were enrolled in the New Jersey Medicaid program between November 1980 and June 1987, filled a first prescription for a glaucoma medication, and were enrolled for a minimum of 15 months following the initial prescription. The authors found that 23% of patients had no prescription for a glaucoma medication filled during a 12-month period following the initiation of therapy. In addition, the prescription refill data indicated that the average number of days without therapy during the year was 112.[98]

In another large, population-based retrospective cohort study, Reardon et al obtained records from the Protocare Sciences Managed Care database of 28,741 patients naïve to glaucoma therapy who were ≥20 years of age and had initiated monotherapy on 1 of 6 commonly prescribed hypotensive agents between July 1996 and June 2002. In this study, the authors reported that at 12 months following the initiation of monotherapy, only 33% of patients prescribed latanoprost had not discontinued therapy and only 19% of those initially prescribed other hypotensive agents had not discontinued therapy.[99]

Nordstrom et al looked at both persistence and adherence in a large, retrospective cohort study using data from the Ingenix Research database, which consists of insurance claims for approximately 8 million members of UnitedHealthcare (UHC). The study cohort included UHC members who

were newly diagnosed with open-angle (n=3623) or suspect glaucoma (n=1677) and received at least 1 dispensing of a topical ocular hypotensive medication between July 1995 and December 2001. Mirroring the results of Reardon et al, nearly one-half of the subjects in this study discontinued all ocular hypotensive medication within 6 months of initial dispensing.[7]

In what is generally considered to be a landmark study in this area, Friedman et al designed the Glaucoma Adherence and Persistency Study (GAPS).[100] One segment of the study analyzed a retrospective pharmacy claims database of almost 14,000 patients prescribed topical ocular hypotensive medication. In this study segment, the primary adherence outcome was medication possession ratio (MPR), which was defined as the days of prescription supply dispensed divided by the number of days between the first and last prescription refill. The primary persistence outcome was a gap analysis based on whether or not the initial prescription was consistently refilled within a calculated period of time based on the days supply within the bottle. On the primary adherence outcome, the mean MPR for the 13,956 patients meeting the inclusion and exclusion criteria was 0.64 while the median MPR was 0.57, where 1.00 would be defined at 100% adherence. On the primary persistence outcome, among the 10,260 subjects who were followed up for at least 1 year after the index prescription, only 10% of subjects were 100% persistent in their use of the initially prescribed glaucoma medication over the initial 12 months, and only 2% of those who were subsequently prescribed a second glaucoma medication were persistent over the same period. The authors also reported that 54% had a gap in refilling the initially dispensed drug and subsequently only 22% of these remained persistent for the remaining portion of the study period.

A number of studies have also found increased drug burden, including both additional glaucoma and nonglaucoma-related medications, to have a negative impact on overall patient compliance with their glaucoma medications. Robin et al examined the effect of adding complexity to a glaucoma medical treatment regimen in a retrospective review of patient records from a national health care provider, which included 4930 patients who had received a prescription for latanoprost between July 1, 2001, and June 30, 2002. Among the subgroup of 1784 patients who subsequently had a second ocular-hypotensive medication added, mean refill intervals for latanoprost were 40.6 days before the addition of a second drug and 47.4 days after the addition of a second drug, a mean increase of 6.7 days. For 22.9% (409/1784) of patients, the interval was increased by >2 weeks (P<.0001). The mean refill interval was longer than that for the 3146 patients who continued on latanoprost monotherapy, which was 41 days.[101]

Persistence and adherence are not the only factors affecting compliance with antiglaucoma medications. Winfield et al reported on interviews with 200 patients who used topical medication for a number of ophthalmic indications, with the largest percentage being glaucoma. In total, 57% of patients admitted having some difficulty administering their drops, with 49% of patients reporting that they missed instilling drops in their eyes either frequently or occasionally. In a series of ability tests, only 20% of patients were able to instill a drop in their eye unaided the first time.[102]

Stone et al recently attempted a more objective approach to this issue by videotaping 173 patients with a minimum of 6 months experience instilling ocular hypotensive drops from either a 2.5-mL or 15-mL bottle. Data were available for 139 patients and among these the group using the 15-mL bottle required an average of 1.8 drops in order to instill 1 drop of medication into the eye, while the figure for the 2.5-mL bottle group was 1.4 drops. Only 31% of the 2.5-mL group and 22% of the 15-mL group achieved all 3 key performance criteria, which included instillation of a single drop, instillation of a drop in the eye, and no touching of the bottle tip to the ocular adnexae.[103]

Other reasons for poor compliance include hearing difficulty, health literacy, physical or cognitive disability, limited financial resources, drug costs, impaired visual acuity, contrast sensitivity, and stereopsis.[104] A separate study showed that 41% of glaucoma patients who are noncompliant indicated that they experience challenges in paying for their medications.[105] Cost as a barrier to adherence is difficult to assess since patients are reluctant to discuss this issue with their physicians. A survey of older adults with chronic illnesses revealed that 66% of patients never informed their clinician in advance that they planned to underuse their medication(s) because of cost concerns, and 35% did not discuss the issue at all.[104]

Other factors that may play a role in poor compliance include disease severity, complicated dosing regimens, level of education, forgetfulness, inconvenience, inability to read the print on the bottle, adverse events, difficulty squeezing the bottle, and difficulty removing the seal.[104]

3. SAFETY/SIDE EFFECTS

Prostaglandin analogues are the most commonly prescribed hypotensive medications for glaucoma in the United States and are the first choice for newly diagnosed patients. This class of drugs has an excellent safety profile with regard to systemic side effects, however they are associated with a number of ocular side effects including conjunctival hyperemia, elongation and darkening of eyelashes, induced iris darkening, and periocular skin pigmentation.[106]

β-blockers are the second most commonly prescribed class of topical glaucoma medications and are still used as first-line therapy for many patients, especially those concerned with the cost of their glaucoma medications. Timolol in its various forms is by far the most commonly prescribed and is a nonselective β-blocker. Ocular side effects such as stinging, burning, redness, discomfort, and foreign body sensation

are reported with β-blockers, but the incidence is relatively low compared to other classes of topical hypotensive medications. A greater concern with these drugs is the potential for systemic side effects, which are similar to those occurring with systemic β-blockers and can be serious and potentially life-threatening in nature. Systemic side effects associated with topical β-blockers can be cardiovascular (eg, arrhythmia, hypertension, cardiac arrest, cardiac failure), pulmonary (eg, cough, bronchospasm, respiratory failure), or CNS (eg, headache, dizziness, confusion) in nature. Nonselective β-blockers are contraindicated in patients who have any number of cardiopulmonary diseases including bronchial asthma and chronic obstructive pulmonary disease (COPD).[107]

Alpha agonists (eg, brimonidine tartrate) and topical carbonic anhydrase inhibitors (eg, dorzolamide, brinzolamide) are more commonly used as adjunctive therapy. Neither alpha agonists nor topical carbonic anhydrase inhibitors are associated with significant incidence of systemic side effects. Ocular side effects are common with alpha agonists and include conjunctival hyperemia, allergic conjunctivitis, and ocular pruritus.[108] Common ocular side effects of topical carbonic anhydrase inhibitors include conjunctival hyperemia, stinging, and irritation.[109]

4. IOP FLUCTUATIONS

Noncompliance with ocular hypotensive drugs can result in large fluctuations in IOP. Large fluctuations in IOP are associated with an increased risk for vision loss as compared to nonintervention.[79,88] Due to noncompliance, drug half-life, and complex dosing schedules, topical medications often do not effectively provide 24-hour control of IOP.[110] Prescription therapy of latanoprost demonstrated a mean IOP fluctuation of 5.2 mm Hg.[111] A subanalysis of patients from AGIS demonstrated that fluctuating IOP increased

the risk for visual field loss.[5] In 2008, another analysis of patients enrolled in AGIS indicated that there is a strong correlation between fluctuating IOP and progressive visual field loss, particularly in patients with lower IOP.[88] In a separate clinical trial, IOP fluctuations of >5 mm Hg have been shown to increase risk for vision loss. Surgical procedures (trabeculectomy and deep sclerotomy) provide statistically significant greater circadian control than drug therapy.[111]

5. OCULAR SURFACE DISEASE

Patients with glaucoma are at higher risk for developing ocular surface disease (OSD) or dry eye, as OSD and glaucoma are most commonly seen in older populations. In addition, glaucoma patients are often being treated with eye drop medications that are preserved with benzalkonium chloride (BAK). Many ocular hypotensive medications contain preservatives, such as BAK, which can have toxic effects on the ocular surface. Long-term compounded exposure to BAK can cause corneal surface damage, resulting in exacerbated symptoms of dry eye.[112] Additionally, the long-term nature of topical treatments in managing OAG exacerbates their toxic effects.

Eye drop medications preserved with BAK may negatively impact vision-related quality of life for patients with glaucoma. A recent cross-sectional study of 101 glaucoma patients found that 59% reported symptoms of dry eye, using the Ocular Surface Disease Index (OSDI).[113] Multivariate logistic regression models extrapolated from the same study showed that each additional eye drop preserved with BAK was associated with an approximate 200% greater likelihood of having abnormal results on the lissamine green staining test. Lissamine green indicates the presence of OSD via staining of corneal/conjunctival surfaces.[113]

D. LASER TRABECULOPLASTY

Laser trabeculoplasty lowers intraocular pressure by using a laser beam to initiate cellular and biochemical changes in the trabecular meshwork to increase aqueous humor outflow. Laser trabeculoplasty can be performed with argon, diode, and frequency-doubled YAG lasers.

Argon laser trabeculoplasty (ALT) uses a thermal laser that causes small contraction burns in the trabecular meshwork. Selective laser trabeculoplasty (SLT) is a newer technology using an Nd:YAG laser to target melanocytes in the trabecular meshwork, creating less thermal damage than ALT. Compared to medications, SLT demonstrates similar IOP reductions, safety, and tolerability, and no issues with compliance/adherence.[114-117]

Laser trabeculoplasty is often used as first-line therapy in patients who are likely to be noncompliant with pharmacotherapy for reasons such as cost, problems with memory, or difficulty with instillation.

In eyes that are naïve to surgery, ALT has been found to provide a clinically significant reduction of IOP (>75% of eyes).[87,118]

At 1 year after laser trabeculoplasty, many patients tend to remain on the same number of medications as before laser trabeculoplasty. Results from long-term studies indicate that 30% to >50% of eyes require additional surgical treatment within 5 years. Failure rates after SLT have been reported in 68% to 74% of patients, with a mean time to failure of 5.5 to 6 months.[119]

In a separate clinical trial of 89 patients with elevated IOP, 100% of patients remained on the same number of medications or increased the number of medications 1 year post treatment with SLT or ALT. More patients in the ALT group than the SLT group required an additional medication at 1 year, 29% and 18%, respectively.[114]

E. FILTERING SURGERY

The vast majority of surgeries performed in the United States for the treatment of open-angle glaucoma are referred to as "filtering" surgeries. These procedures involve incising the portion of the conjunctiva covering the sclera, as well as the sclera itself, in order to create an alternate pathway for the drainage of aqueous humor. These procedures are relatively to highly invasive and are associated with significant complication rates. Consequently, surgical glaucoma procedures are generally reserved for patients with advanced disease who can no longer be controlled with medication or laser therapy. The reported outcomes on these procedures generally reflect this patient population. Outcomes in this monograph concerning the iStent are focused on the mild-to-moderate open-angle glaucoma population and thus cannot be directly compared to reported outcomes for filtering procedures.

There is a significant downside to bypassing the eye's natural outflow mechanisms and creating an alternate pathway, or artificial bypass: Aqueous outflow can increase to the point that IOP can fall dangerously low. This is referred to as hypotony and is generally defined as IOP <5 mm Hg and is essentially deflation of the eyeball. Because a minimum level of eye pressure is what keeps internal ocular tissues in their normal positions and functioning properly, hypotony can lead to serious complications such as flattened anterior chambers with choroidal and retinal detachments and suprachoroidal hemorrhage.

1. TRABECULECTOMY

Trabeculectomy is the most common surgical filtration procedure performed for the treatment of open-angle glaucoma and is considered the gold standard for glaucoma surgery. A trabeculectomy creates a small flap in the sclera in order to access the anterior chamber and allow aqueous humor to flow out. This flow creates a filtration bleb, or reservoir, under the conjunctiva from which the aqueous humor is absorbed into nearby blood vessels. Trabeculectomy often reduces IOP and the need for medical treatment. In the Collaborative Initial Glaucoma Treatment Study (CIGTS), a large trial in which newly diagnosed patients were randomized to either medications or trabeculectomy, mean IOP in trabeculectomy group was reduced by approximately 50% to between 14 and 15 mm Hg over 5 years of follow-up. In addition, mean IOP in the trabeculectomy group was consistently 2 to 3 mm Hg lower than in the medications group throughout the follow-up period.[81] However, as reported in the Advanced Glaucoma Intervention Study, the best estimate of the failure rate of trabeculectomy alone or combined with medical therapy in a previously unoperated eye is approximately 30% in African American patients and 20% in Caucasian American patients over a 10-year period.[87]

The key drawback to trabeculectomy is filtration-bleb problems, which can occur in up to 43% of patients within 1 year postoperatively.[120] The use of adjunctive medicines, such as mitomycin C and 5-fluorouracil, to reduce subconjunctival scarring improves surgical outcome but also increases the incidence of complications, such as persistent hypotony, hypotony maculopathy, keratitis, ocular surface disease, bleb leaks, blebitis, endophthalmitis and scleral melting, and loss of vision.[121-131] Complications of penetrating filtering procedures include infection, inflammation, vision loss, bleb leak, bleb encapsulation, hypotony, cataract, and the need for repeat surgery.[6,83,132] In addition, the documented annual risk of endophthalmitis associated with filtering blebs, a serious adverse event which can result in blindness, is 1% to 2%.[124,133]

2. AQUEOUS SHUNTS

a) Standard aqueous shunts

Filtering surgery can also be accomplished by implanting devices known as aqueous shunts. All standard "*ab externo*" aqueous shunts, which are also known as tube shunts, glaucoma

drainage devices, and setons, consist of a tube that diverts aqueous humor to an end plate located in the equatorial region of the eye. All standard aqueous shunts are implanted in *ab externo* procedures. This means that an incision is made from the outside of the eye through the conjunctiva and sclera in order to place the implant. The primary resistance to flow through these devices occurs across the fibrous capsule that develops around the end plate. Aqueous shunts differ in their design with respect to the size, shape, and material from which the end plate is made. Aqueous shunts can be further subdivided into valved and nonvalved shunts, depending on whether or not a valve mechanism is present to limit flow through the shunt if the IOP becomes too low.

Examples of nonvalved implants are[80]:

1. THE BAERVELDT GLAUCOMA IMPLANT (ABBOTT MEDICAL OPTICS, SANTA ANA, CA)

2. THE MOLTENO IMPLANT (MOLTENO OPHTHALMIC LTD., DUNEDIN, NEW ZEALAND)

Examples of valved implants are[80]:

1. THE AHMED GLAUCOMA VALVE (NEW WORLD MEDICAL, INC., RANCHO CUCAMONGA, CA)

2. THE KRUPIN IMPLANT (EAGLE VISION, INC., MEMPHIS, TN)

The plate portion of standard aqueous shunts available in the United States range from 14 mm by 14 mm to 13 mm by 32 mm, with footprints ranging from 175 mm^2 to 350 mm^2.
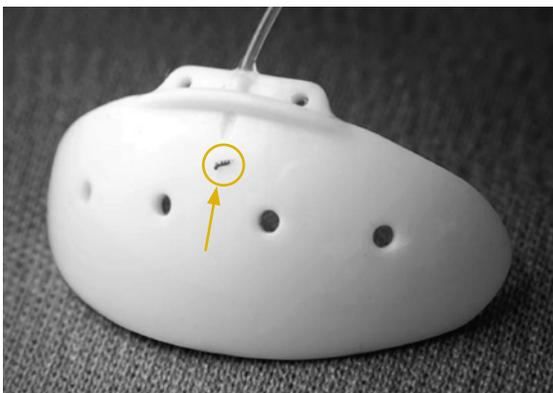
Figure 2. iStent Trabecular Micro-Bypass positioned on a Baerveldt® Glaucoma Implant.

A systematic review of the literature was published in 2005 covering the 4 most frequently used, and reported on, aqueous shunt devices: Molteno, Baerveldt, Ahmed, and Krupin-Denver.[134] (NOTE: The Krupin-Denver device is no longer sold.) As is the standard in the majority of studies evaluating glaucoma devices, surgical success in this review was defined as postoperative IOP of ≤21 mm Hg and ≥5 mm Hg with or without medications and without devastating complications such as suprachoroidal hemorrhage or endophthalmitis leading to visual loss. Using these criteria, the overall surgical success rate ranged between 72% and 79% among the 4 devices with no statistical differences at the last follow-up visit (P=0.94).

All of the aqueous shunts in this literature review were effective at lowering IOP. Preoperative IOP for the 4 devices ranged from 30.8 mm Hg to 42.1 mm Hg. Postoperative IOP ranged between 13.8 mm Hg and 17.1 mm Hg on between 0.8 and 1.5 medications. Average percentage reduction in IOP ranged from 51% to 62%. However, while the implantation of aqueous shunts can provide dramatic reductions in IOP, this level of efficacy comes with a relatively high rate of serious, device-related adverse events. In this review article, incidence of suprachoroidal hemorrhage ranged from 3% to 8%, chronic hypotony ranged from 2% to 6%, and diplopia ranged from 2% to 9%. Consequently, like trabeculectomy, aqueous shunts are generally reserved for patients with severe or end-stage glaucoma, and the labeling for these devices is consistent with this usage.

In a comprehensive review of the types of complications frequently associated with standard aqueous shunts and their incidence rates in 2000, the following common complications were noted (incidence in parentheses)[135]:

1. HYPOTONY/FLAT ANTERIOR CHAMBER (3.5% TO 27%)

2. MACULOPATHY OF HYPOTONY (1.3%)

3. TUBE OBSTRUCTION (6% TO 11%)

4. CHOROIDAL EFFUSION (7% TO 33%)

5. SUPRACHOROIDAL HEMORRHAGE (4.2%)

6. VITREOUS HEMORRHAGE (1.3% TO 7%)

7. MOTILITY DISORDERS (EG, DIPLOPIA) (0.3% TO 21%)

8. UVEITIS (0.5% TO 9.3%)

9. CATARACT FORMATION AND PROGRESSION (9.9% TO 12%)

10. EROSION OF TUBE OR EPISCLERAL PLATE THROUGH THE CONJUNCTIVA (0.5% TO 4.3%)

11. RETINAL DETACHMENT (2% TO 5%)

12. WOUND LEAK AND DEHISCENCE (1.5%)

13. EPIRETINAL MEMBRANE (IE, MACULAR PUCKER) (0.3%)

b) Ex-PRESS™ Glaucoma Filtration Device

The Ex-PRESS™ Glaucoma Filtration Device is similar to standard *ab externo* aqueous shunts in that it diverts aqueous humor via an alternate or artificial pathway, rather than through the eye's natural, physiological outflow pathways. It is also similar to other *ab externo* aqueous shunts in that it is implanted via an *ab externo* procedure in which the conjunctiva and sclera are incised in order to place the implant. The Ex-PRESS shunt differs from other *ab externo* aqueous shunts in that it does not include a plate. However, the procedure for implanting the Ex-PRESS shunt is like that for trabeculectomy and, similar to trabeculectomy, results in a filtering bleb. Thus, the risk of bleb-related infections remain present with this device.

A prospective, randomized, controlled, single-site study (n=80) compared implantation of the Ex-PRESS shunt to trabeculectomy.[136]

Complete success was defined as an IOP of >4 mm Hg and ≤18 mm Hg without use of antiglaucoma medications. At the 1-year follow-up visit, complete success was achieved by 82% of the Ex-PRESS group and 48% of the trabeculectomy group. Complications and postoperative interventions were similar between the 2 groups. Complications in the shunt group included early hypotony (16%), shallow anterior chamber (20%), and choroidal detachment (8%). In addition, 1 eye required shunt replacement due to shunt malposition.

In a retrospective, comparative case series (n=50), patients implanted with the Ex-PRESS shunt were compared with matched control eyes undergoing trabeculectomy. Success was defined as IOP of ≥5 mm Hg and ≤21 mm Hg with or without glaucoma medications and without further glaucoma surgery or removal of implant. At 15 months, the success rate was similar in both groups (86% in the Ex-PRESS group vs 84% in the trabeculectomy group). Complications were lower in the Ex-PRESS group than in the trabeculectomy group and included choroidal effusion (8%), of which 1 case required surgery in order to resolve, bleb leak (6%), hypotony maculopathy (4%), hyphema (4%), flat anterior chamber (2%), and 1 case of endophthalmitis, a serious complication, which required removal of the device.

Direct comparisons of efficacy and safety between the aqueous shunts and the iStent Trabecular Micro-Bypass stent should not be made because the devices are intended for 2 different patient populations. The iStent device is intended for use in adult patients with mild-to-moderate glaucoma. The aqueous shunts are intended for use in patients with advanced or end-stage glaucoma for whom medications are no longer effective and, in most cases, for whom conventional surgical options have already been tried. Thus, not surprisingly,

preoperative IOPs as well as postoperative complication rates are significantly higher in patients who receive *ab externo* aqueous shunts in published studies.

3. NONPENETRATING FILTERING SURGERY

Nonpenetrating glaucoma surgery includes deep sclerectomy, viscocanalostomy, canaloplasty, *ab interno* excimer laser trabeculostomy, and *ab interno* microelectrocautery of a portion of the trabecular meshwork and inner wall of the trabecular meshwork.[138] The reported advantage of nonpenetrating surgery is that it does not create a full-thickness macroperforation into the anterior chamber. Deep sclerectomy generally relies on a transcleral filtration bleb.

Viscocanalostomy refers to the injection of sodium hyaluronate to dilate portions of Schlemm's canal. Viscocanalostomy may be a blebless procedure that drains the aqueous humor into an internal reservoir without penetrating the sclera.[139]

Canaloplasty refers to the use of a flexible microcannula inserted into Schlemm's canal to deliver high-viscosity sodium hyaluronate through the circumference of the canal and install a trabecular tensioning suture to restore and maintain its patency.[140]

Patients who underwent canaloplasty experienced a 36% reduction (-8.6 mm Hg) in mean IOP and a mean decrease of 1.3 medications. However, 21% experienced procedure failure with a 20% incidence of bleb formation.[141]

In a separate study, canaloplasty combined with phacoemulsification cataract surgery significantly reduced IOP vs baseline. Patients showed a 44% reduction (-10.7 mm Hg) in mean IOP and a mean decrease of 1.3 medications.[140] Most surgical complications resolved within 2 months of surgery, although microhyphema was an early transient finding (33.6%).[140] In addition, hypotony, iris prolapse, and Descemet Membrane Detachment (DMD) are serious adverse events related to canaloplasty. Since market approval, bilateral Descemet Membrane Detachment has also been reported.[140,141]

A study of deep sclerectomy with or without a collagen implant to maintain patency resulted in a complete success rate (IOP <21 mm Hg without medication) of 38% in the noncollagen implant group and 69% in the group with the implant at 48 months.[142] Patients were taking more than 2 medications before surgery, and this was significantly reduced postsurgery in the collagen group (P=.001). Complications were similar in both groups.

F. CYCLODESTRUCTIVE SURGERY

Cyclodestructive surgical procedures lower IOP by ablating the ciliary processes. This lowers the production of aqueous humor and subsequently the IOP. This approach differs from conventional filtration surgery, which increases aqueous outflow. Traditionally, cycloablation has been performed transclerally (transcleral cyclophotocoagulation, or TCP). Endoscopic cyclophotocoagulation (ECP) uses a diode laser equipped with an endoscope. ECP provides direct visualization of the ciliary processes, which permits a more targeted approach.[143]

ECP is most commonly performed in conjunction with cataract surgery. In a randomized prospective study of 58 eyes with a mean follow-up of 2 years, ECP and phaco resulted in a mean IOP decrease of 29% (-8.8 mm Hg) and a mean decrease of 1.2 medications. However, 10% of patients underwent trabeculectomy.[144]

ECP is an intraocular procedure with the attendant risks of penetrating surgeries. Potential complications include endophthalmitis, choroidal hemorrhage, retinal detachment, cystoid macular edema, and high rate of development of cataracts.[143,145] ECP remains controversial as a primary procedure.

V. COMBINED CATARACT AND GLAUCOMA

Coexistent cataract and open-angle glaucoma is common and found primarily in the elderly population. The incidence of both open-angle glaucoma and cataract increases sharply with age, and these conditions are both relatively common in the elderly population. The cumulative incidence of nuclear cataract increased from 2.9% in persons aged 43 to 54 years at baseline to 40% in those aged 75 years or older. For cortical and posterior subcapsular cataract, the corresponding values were 1.9% and 21.8% and 1.4% and 7.3%, respectively.[146] With regard to glaucoma, among whites, the prevalence of glaucoma among 40-year-olds is between 0.25% and 0.50% but increases to nearly 4% by age 75. Among blacks, prevalence is approximately 2% at age 40 but increases to approximately 10% by age 75.[37]

An analysis of a statistically representative sample of the United States Medicare database from 2002 to 2007 found that among patients undergoing cataract surgery, 12.9% also had a diagnosis of open-angle glaucoma and an additional 7.6% had a diagnosis of ocular hypertension.[147]

Patients diagnosed with both open-angle glaucoma and cataract are considered a distinct patient population within ophthalmology. In 2003, the Agency for Healthcare Research and Quality (AHRQ) published a technology assessment entitled "Treatment of Coexisting Cataract and Glaucoma."[148] The opening paragraph of this assessment reads as follows:

Cataract and glaucoma are both common conditions and are often present in the same patient. Cataract surgery is the most commonly performed surgical procedure on Medicare beneficiaries.[149] Approximately 1.6 million cataract surgeries were performed on Medicare beneficiaries in 1998. Open-angle glaucoma affects at least 2.5 million individuals in the United States.[150] The total direct cost expenditures for glaucoma therapy have been estimated at $1.56 billion per year.[151] Although guidelines exist for the indications for cataract surgery in the otherwise healthy eye and for glaucoma surgery in eyes with glaucoma, controversy exists concerning the indications for surgery when both cataract and glaucoma are present. In addition, there is no clear consensus about the appropriate timing of the surgery for each condition, or about the best surgical technique. At the present time, there is no agreement concerning the optimal management of these disorders when coexistent.

A total of 919 articles were identified in the peer-reviewed literature on the topic of coincident glaucoma and cataract, and 131 of these were reviewed for the technology assessment.

Recent medical innovations now enable ophthalmic surgeons to offer minimally invasive procedures to patients with combined cataract and OAG that can control IOP, reduce or eliminate dependence on drug therapy, and avoid the risks associated with complex, invasive surgical interventions. In the past there has been a lack of consensus among surgeons regarding the management of coexisting cataract and glaucoma. A systematic review of 39 articles provided good evidence that long-term IOP is lowered more by combined glaucoma and cataract operations than by cataract operations alone.[152] On average, the IOP was found to be 3 to 4 mm Hg lower in the combined groups, with fewer medications required.

Numerous studies have shown that cataract surgery alone results in a permanent, long-term statistically significant reduction in intraocular pressure and medication usage in patients diagnosed with open-angle glaucoma.[153-159]

Based on the evidence in the peer-reviewed literature, the American Academy of Ophthalmology states the following in its "Preferred Practice Pattern for Primary Open-Angle Glaucoma"[80]:

> Patients with primary open-angle glaucoma who have a visually significant cataract have a range of options to consider. If IOP control is at target on one or few medications, cataract surgery alone may be adequate, with the additional benefit that it may lower IOP slightly....Cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2 mm Hg on average.

In addition, the American Glaucoma Society recently issued its "Position Statement on New Glaucoma Surgical Procedures,"[160] which states:

> Some categories of new surgical devices and techniques are utilized at the time of concomitant cataract surgery. Cataract surgery alone has been shown to lower intraocular pressure. A control group of patients with similar entry criteria undergoing cataract surgery alone may be appropriate for these technologies.

Thus, cataract surgery alone is an appropriate comparator in a randomized, controlled trial evaluating a novel device for the treatment of mild-to-moderate glaucoma.

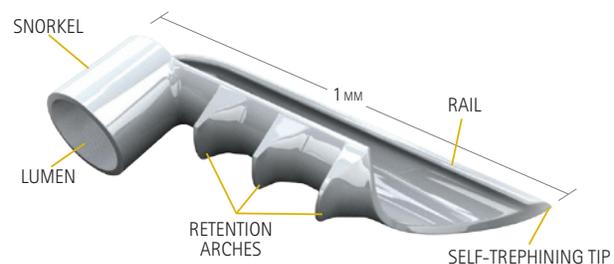# VI. iSTENT® TRABECULAR MICRO-BYPASS STENT

A. INDICATIONS FOR USE

The iStent Trabecular Micro-Bypass Stent (Models GTS 100R and 100L) is indicated for use in conjunction with cataract surgery for the reduction of IOP in adult patients with mild-to-moderate open-angle glaucoma currently treated with ocular hypotensive medication. The iStent is the first glaucoma device to be approved for use in patients with mild-to-moderate open-angle glaucoma, which encompasses the great majority of patients who have been diagnosed with open-angle glaucoma.

According to an analysis of the Medicare Statistical Analysis file for the years 2003 to 2007, 12.9% of Medicare beneficiaries in the United States undergoing cataract surgery had previously received a diagnosis of open-angle glaucoma. For patients who have challenges with or who are not candidates for drug therapy, iStent has been shown to safely control IOP while eliminating many patients' need to take glaucoma medication.

B. DESIGN AND SPECIFICATIONS

The Glaukos iStent Trabecular Micro-Bypass Stent is the smallest medical device known to be implanted in the human body and weighs just 60 µg. The iStent device is manufactured from nonferromagnetic titanium (Ti6Al4V ELI) and is heparin coated in order to promote self-priming and facilitate outflow. The stent is a single-piece design, 1.0 mm in length, and 0.33 mm in height with a snorkel (inlet) length of 0.25 mm and snorkel bore diameter of 120 µm. The iStent has an "L"-shaped structure with the snorkel on the short side which resides in the anterior chamber, and which opens to the half-pipe body which resides in Schlemm's canal (see figure 3). The retention arches on the closed side of the body serve to securely fixate the device in Schlemm's canal. The open half-pipe part of the body is against the outer wall in order to access collector channels. The dimensions of the iStent device are customized for a natural fit within the 270-µm Schlemm's canal space. During the manufacturing process, the stent is loaded onto the end of a disposable insertion instrument, and the "system" is placed in a high-impact polystyrene (HIPS) tray, which is then placed into a PETG blister tray, sealed with a Tyvek® lid, and then gamma-sterilized. The sterility expiration date appears on the outside of the unit carton (the shelf-life is 3 years from the date of sterilization).

Figure 3. Glaukos iStent® Trabecular Micro-Bypass Stent view of open stent body (right stent GTS 100R)

Figure 4. Glaukos Inserter

The implant is provided to the surgeon in a sterile, preloaded configuration, thereby minimizing operating room manipulation and allowing for insertion into Schlemm's canal through the trabecular meshwork using an *ab interno* stent placement approach. The inserter has been designed by Glaukos to hold the implant and to disengage from the implant once the implant has been inserted into Schlemm's canal. The inserter also has reacquisition capability. Two model numbers (GTS100L and GTS100R) are available. The last characters of these model numbers (L and R) correlate to a left-flow stent and a right-flow stent. The stents are identical except the body faces opposite directions in order to facilitate nasal stent placement. Model GTS100L is designed for the left eye and Model GTS100R for the right eye.
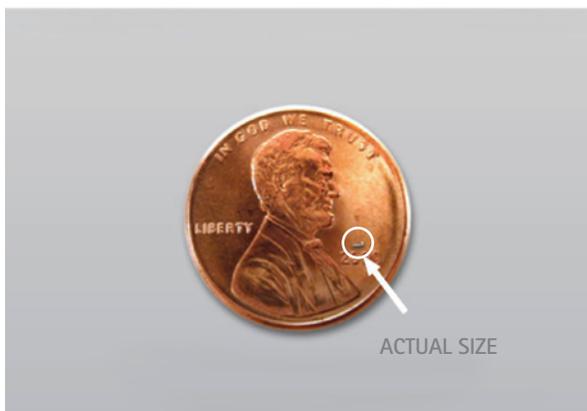

ACTUAL SIZE

Figure 5. Actual size of iStent implant compared to a penny.

C. MECHANISM OF ACTION

The iStent device is the first and only implantable device that improves aqueous outflow through the natural physiologic outflow pathway. When the device is implanted into the trabecular meshwork, it stents open that section of the ocular anatomy and allows aqueous humor to flow from the anterior chamber into Schlemm's canal. Research in the physiology of the trabecular meshwork in normal and diseased eyes suggests the trabecular meshwork is the primary site of aqueous outflow and increased outflow resistance, and thus reduced outflow facility in open-angle glaucoma.[11,12-14,16] Up to 75% of total resistance to aqueous humor outflow is found in the juxtacanalicular tissue of the trabecular meshwork.[16,161,162] Diseased trabecular meshwork causes significant increases in outflow resistance resulting in elevated IOP.[160]

Collector channels also have an important role in controlling IOP, as these structures facilitate the outflow of aqueous humor. There are numerous collector channels leaving Schlemm's canal at irregular intervals. The largest congregations of collector channels are found in the infranasal quadrants. The infranasal quadrants are optimal sites to create a patent bypass in order to maximize outflow through Schlemm's canal. Increasing outflow through the lower nasal quadrant has a significant impact on increasing outflow and lowering IOP as compared to targeting quadrants with lower collector channel congregations.[162,163]

The *ab interno* placement of the iStent device in the infranasal quadrant is designed to maximize aqueous humor outflow due to the high presence of collector channel congregations in the infranasal quadrants (Figure 6). The physiological preservation of the trabecular meshwork ensures a natural episcleral back pressure of 8 to 11 mm Hg, with minimal risk of hypotony.[16]
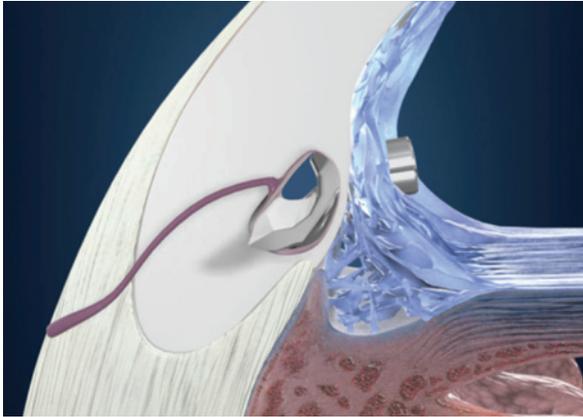
Figure 6. Schematic of the iStent implant in relation to the structures of the outflow path. iStent restores continuous physiologic outflow by creating a patent bypass between the anterior chamber and Schlemm's canal.

D. SURGICAL TECHNIQUE

Cataract surgery with IOL implantation should be performed first followed by implantation of the iStent. Because the iStent is designed for nasal placement, cataract surgery should be performed through a temporal incision. An intracameral miotic should be injected if the angle needs to be deepened following cataract surgery.
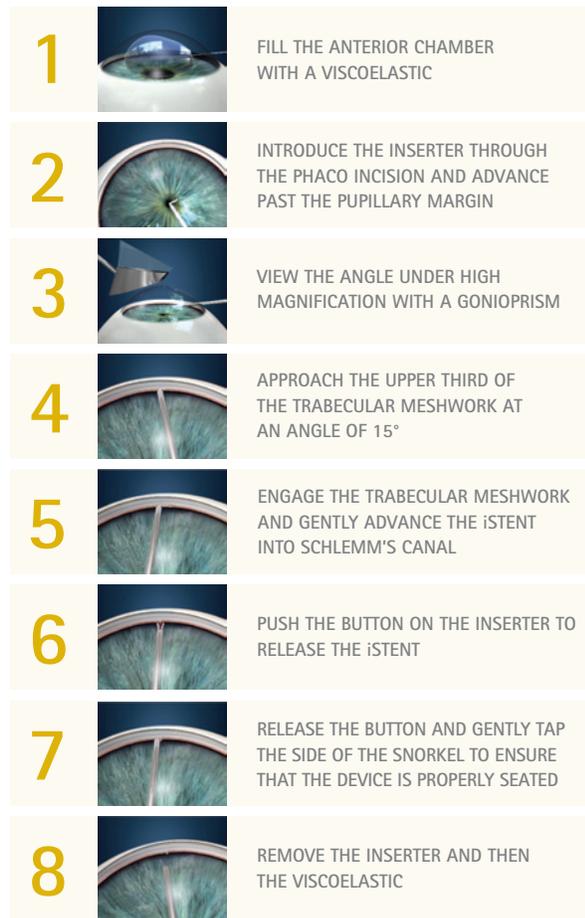
After selecting the model for implantation (ie, GTS100L or GTS100R), the peel pouch containing the iStent Trabecular Micro-Bypass Stent System is opened onto the sterile field. The surgeon grasps the inserter with his or her index finger on the release button. The release button faces up and the surgeon ensures that the orientation of the stent on the inserter is appropriate for the desired nasal implantation.

After inspecting the angle with a gonioprism to ensure a good view at the implant location, the surgeon places a gonioscope on the cornea and repositions the surgical microscope and the patient's head as needed to visualize the trabecular meshwork.

Viscoelastic is injected into the anterior chamber to assist with chamber maintenance. The stent is then inserted through the same temporal incision that was used to extract the cataract and place the intraocular lens. With the stent on the tip of the inserter, the anterior chamber is traversed with the inserter to approximately the pupillary margin. After placing the gonioprism into the desired position, the surgeon locates the trabecular meshwork, then gently slides the stent tip through the trabecular meshwork and into Schlemm's canal at the nasal position with the tip of the implant directed inferiorly. The stent is inserted so that the rails are located on the back wall of Schlemm's canal and the stent body is parallel to the iris plane. The surgeon releases the stent by pushing the button on the inserter and then gently taps the side of the snorkel with the inserter to align the body of the stent in Schlemm's canal and verifies that the inlet of the snorkel is visible in the anterior chamber.

After withdrawing the inserter, the surgeon irrigates the anterior chamber with BSS to remove viscoelastic and any refluxed blood; and the anterior chamber is inflated with saline solution as needed to achieve physiologic pressure.

SURGICAL PROCEDURE

1		FILL THE ANTERIOR CHAMBER WITH A VISCOELASTIC
2		INTRODUCE THE INSERTER THROUGH THE PHACO INCISION AND ADVANCE PAST THE PUPILLARY MARGIN
3		VIEW THE ANGLE UNDER HIGH MAGNIFICATION WITH A GONIOPRISM
4		APPROACH THE UPPER THIRD OF THE TRABECULAR MESHWORK AT AN ANGLE OF 15°
5		ENGAGE THE TRABECULAR MESHWORK AND GENTLY ADVANCE THE iSTENT INTO SCHLEMM'S CANAL
6		PUSH THE BUTTON ON THE INSERTER TO RELEASE THE iSTENT
7		RELEASE THE BUTTON AND GENTLY TAP THE SIDE OF THE SNORKEL TO ENSURE THAT THE DEVICE IS PROPERLY SEATED
8		REMOVE THE INSERTER AND THEN THE VISCOELASTIC

Figure 7. iStent is inserted *ab interno* through the phaco incision and can be performed under topical anesthesia.

E. CLINICAL TRIALS

1. INVESTIGATIONAL DEVICE EXEMPTION (IDE) PIVOTAL TRIAL

The majority of the devices currently marketed in the United States for the treatment of glaucoma have been cleared under the 510(k) process. Unlike standard *ab externo* shunts for refractory glaucoma which are Class II devices, the iStent is a Class III implantable device. As a result, the iStent was required to undergo the more rigorous premarket approval (PMA) process.

Consequently, for this new device, the FDA required a large comparative study to be conducted in subjects with primary open-angle glaucoma already undergoing cataract surgery, in order to measure the incremental effect from iStent implantation over that of cataract surgery alone, and to determine the potential benefit of combining two therapeutic treatments into one surgical event. Subjects were randomized into one of two treatment groups— stent implantation in conjunction with cataract surgery or cataract surgery alone—and their outcomes were assessed vis-à-vis endpoints well-recognized as guidelines for surgical success in glaucoma practice and clinical trials.[165-173]

The study was a prospective, randomized, open-label, multicenter, controlled US IDE clinical trial conducted at 29 US investigational sites. Adult subjects were enrolled who were in need of cataract surgery and who had mild or moderate open-angle glaucoma confirmed by gonioscopy with visual field or nerve pathology characteristic of glaucoma, with IOP ≤24 mm Hg and on 1 to 3 ocular hypotensive medications. After a washout of ocular hypotensive medication, IOP was required to be ≥22 mm Hg and ≤36 mm Hg during normal office hours.

Postoperative ocular hypotensive medication, as per the study protocol, was to be added for IOP >21 mmHg or for visual field or optic nerve findings.

The primary efficacy outcome measure was IOP ≤ 21 mm Hg without ocular hypotensive medication 1 year postoperatively. The proportion of subjects meeting this endpoint was compared between the treatment and control groups. A ≥20% reduction in IOP from baseline without medication at 1 year postoperatively was the secondary efficacy outcome. Similar to the primary endpoint, the proportion of subjects that met this endpoint was compared between groups.[174]

a) Enrollment and Demographics

A total of 240 eyes were enrolled in the randomized portion of the study. The highest enrolling site accounted for less than 15% of subjects; 10 sites enrolled a minimum of 10 subjects. Of the 240 enrolled eyes, 117 were randomized to receive iStent implantation in conjunction with cataract surgery. Of these, 111 were implanted with stents. Among the six subjects who did

not receive the stent, four had complications associated with cataract surgery, one was not implanted due to inability to implant the stent, and one was terminated from the study prior to surgery. A total of 123 subjects were randomized to receive cataract surgery only, and 117 of these proceeded with cataract surgery. Among the six subjects randomized to this group who did not undergo surgery, four were terminated because consent was withdrawn prior to surgery, one was terminated due to baseline exam failure and one was terminated from the study prior to treatment. Follow-up at the 12-month visit was excellent with 97% of subjects presenting in the treatment group and 99% presenting in the control group.

Overall, there were no differences between the two groups in terms of demographics or preoperative characteristics. The mean age in the study was 73 years, and 84% were 65 years of age or older. The subjects enrolled in this trial had moderate glaucomatous disease and a mean (medicated) IOP of 18.4 mm Hg $\pm$ 3.2 mm Hg. There were no differences in preoperative use of topical ocular hypotensive medications with regard to either type or number. Prior to the required preoperative medication washout, the mean number of medications was 1.5 $\pm$ 0.6. Following washout, mean IOP was 25.4 $\pm$ 3.6 mm Hg.

In addition, 50 additional patients were enrolled in a nonrandomized cohort in order to collect additional safety data.

b) **Efficacy**

A higher proportion of subjects in the iStent plus cataract surgery group achieved the primary efficacy endpoint of an IOP ≤21 mm Hg without ocular hypotensive medications at 12 months compared to the cataract surgery only group (68% vs 50%, respectively). This difference was clinically and statistically significantly different (P=.004).[175]

PERCENTAGE OF PATIENTS WHO SUSTAINED IOP ≤21 mm Hg WITHOUT MEDICATION USE[174]
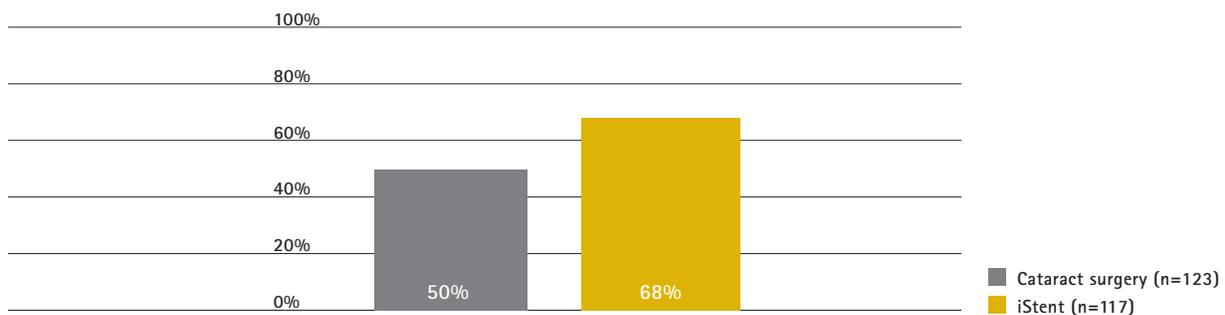
Figure 8. In a 12-month prospective, randomized, multicenter study of 240 eyes, 68% of eyes that received iStent remained medication-free while sustaining target IOPs of ≤21 mm Hg vs only 50% of those that underwent cataract surgery alone (P=.004).

A higher proportion of subjects in the iStent plus cataract surgery group achieved the secondary efficacy endpoint of IOP reduction ≥20% without ocular hypotensive medications at 12 months compared to the cataract surgery only group (64% vs 47%, respectively). This difference was also clinically and statistically significantly different (P=.010)[175] (Figure 9).

PERCENTAGE OF PATIENTS WHO SUSTAINED A ≥20% REDUCTION IN IOP WITHOUT MEDICATION USE[174]
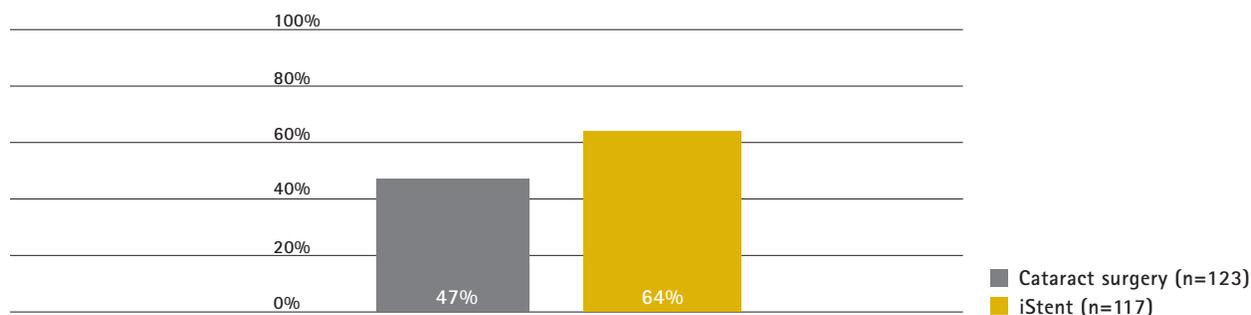

Figure 9. In a 12-month prospective, randomized, multicenter study of 240 eyes, 64% of eyes that received iStent remained medication-free while sustaining a mean IOP reduction of ≥20% vs only 47% that underwent cataract surgery alone (*P*=.010).

The proportion of subjects in the iStent plus cataract group meeting both efficacy endpoints exceeded that for the cataract surgery alone group at all follow-up visits between three and twelve months. The same held true with regard to the proportion of subjects in the iStent plus cataract surgery group achieving IOP ≤18 mm Hg without ocular hypotensive medications.[174]

Postoperative medication use showed a similar trend in that ocular hypotensive medications were added later in the postoperative period and used in a lower proportion of iStent plus cataract patients at every postoperative interval compared to patients in the cataract only group. A Kaplan-Meier analysis illustrates these differences between groups (*P*<.001) (Figure 10). During the first year of follow-up, less than one-quarter of iStent plus cataract patients were on medications at all visits with only 15% on medications at month 12. In comparison, 37% of the cataract only subjects were on medication at the one week postoperative visit and this was virtually unchanged at the one year follow-up visit where 35% of cataract only patients were taking medications. The difference between groups in medication use at month 12 was significant (*P*=.001).

TIME FROM SURGERY TO FIRST REPORT OF MEDICATION USE[174]

TIME TO FIRST POSTOPERATIVE EXAM OF MEDICATION, ITT POPULATION (DAYS FROM OPERATION)
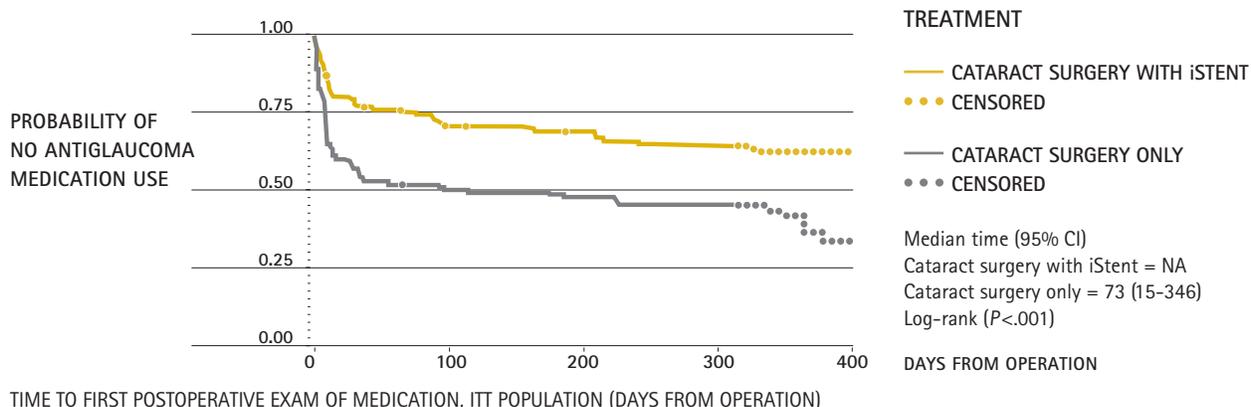
Figure 10. Patients had a significantly greater likelihood of remaining medication-free with iStent vs cataract surgery alone (*P*<.001).

Patients who received iStent achieved a mean 33% reduction in IOP and a reduction from 1.5 medications pre-op to 0.2 medications post-op with 50% less medication than patients who underwent cataract surgery alone. More than twice as many patients who had cataract surgery alone required medication vs the iStent group (*P*=.001) (Figure 11).

PERCENTAGE OF PATIENTS ON OCULAR HYPOTENSIVE MEDICATIONS[174]

Cataract surgery (n=123)
iStent (n=117)
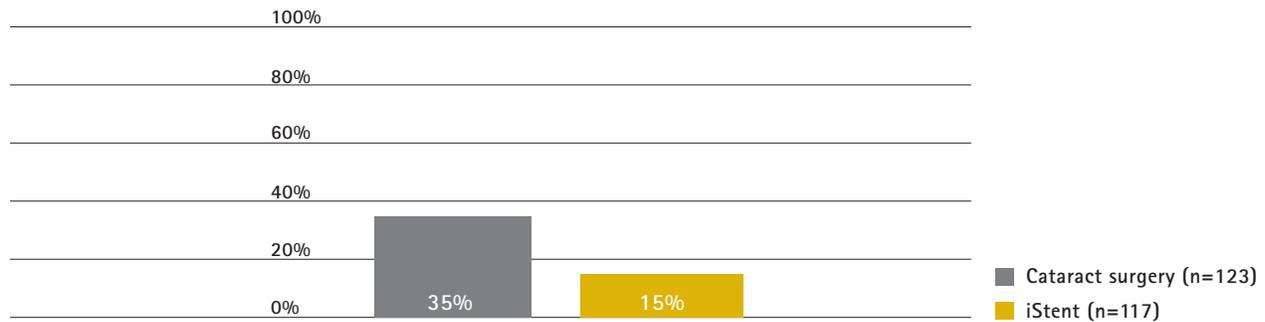
Figure 11. More than twice as many eyes in the cataract surgery alone group (35%) were on ocular hypotensive medications vs those in the iStent group (15%). This difference was significant (*P*=.001).

c) Safety

Early postoperative ophthalmic sequelae typical of cataract surgery occurred in both groups and included corneal edema, trace folds/striae, inflammation, epithelial defect and discomfort. One case of transient hypotony was reported during the first 24 hours and resolved without intervention by the 1-day postoperative visit. The adverse events that occurred most often were similar in both treatment groups. Obstruction of the stent was reported in 4% (n=5) cataract plus stent subjects with four of these cases occurring within the first postoperative month. Four of the five subjects had a subsequent intervention to resolve the obstruction and one was deemed mild with no action required; no persistent sequelae occurred at subsequent follow-up visits. There was one adverse event in each group deemed severe (BCVA loss following stroke in the iStent group and BCVA loss following vitrectomy for macular traction, macular hole and macular edema in the control group) and each of these was judged to be not study related by investigators. The overall safety profile of eyes undergoing iStent plus cataract surgery was similar to that of eyes undergoing cataract surgery alone with no unanticipated adverse device effects reported.[174]

	CATARACT SURGERY ALONE (n=122)	iSTENT PLUS CATARACT SURGERY (n=111)
BCVA LOSS >1 LINE AT 12 MONTHS	5%	3%
STENT OBSTRUCTION	N/A	4%
POSTERIOR CAPSULAR OPACIFICATION	7%	3%
BLURRY VISION OR VISUAL DISTURBANCE	5%	1%
IRITIS	5%	1%

Excerpts from complete listing of study safety population

Table 3. The most frequent adverse events were similar in both groups.

Patients who present for cataract surgery have an expectation of improved postoperative best corrected visual acuity (BCVA). The vast majority of patients in both groups experienced improvement versus their baseline BCVA and this improvement persisted throughout the first year of follow-up. There were no differences between the iStent plus cataract surgery group and the cataract only group regarding proportion of subjects achieving 20/20 or better or 20/40 or better BCVA at either baseline or at any time point during the first year of follow-up. A total of

97% eyes in the iStent plus cataract group vs 95% in the cataract surgery only group reported with improved BCVA (including within 1 line of preoperative BCVA).
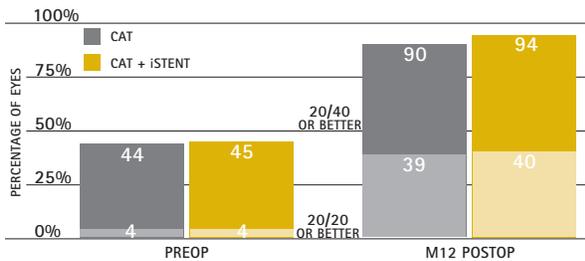
Figure 12. BVCA outcomes at 12 months were similar for both groups.

d) Discussion of IDE Study Results

Glaucoma is a serious, progressive, and incurable disease of widespread significance in the United States. To date, no treatment has been shown to offer restoration of vision. Thus, once diagnosed, glaucoma management aims to delay potentially permanent visual deterioration.

Various medical and surgical therapies available to delay disease progression all have significant limitations in either safety or efficacy or both. The challenges to optimum pharmacotherapy are many.[35,83,99,103,118,176-179] Even when administered correctly, medication is often replete with significant side effects, including ocular inflammation and discomfort; nonocular complications involving cardiovascular, respiratory, and central nervous systems; and long-term diminished efficacy. Laser trabeculoplasty has been shown to provide clinically significant IOP reduction in over 75% of eyes.[87,118] However, failure rates after SLT have been reported in 68% to 74% of patients with a mean time to failure of 5.5 to 6 months.[119] Although SLT may be repeated, there are limits to the number and the effect of subsequent treatments. Incisional surgery is associated with numerous complications, including significant risk of postoperative infection, vision loss, hypotony, surgical intervention, and continued destruction of available ocular tissue. Moreover, patients treated with trabeculectomy, long considered the surgical treatment of choice for glaucoma, remain vulnerable to potentially devastating complications from infection indefinitely following surgery and in subsequent years.[124,133]

Several in vitro studies have reported that a singular trabecular bypass reduces intraocular pressure and increases aqueous humor outflow facility.[180-181] Consistent with these studies, the iStent, when implanted in an *ab interno* procedure, improves aqueous outflow by creating a patent channel through the trabecular meshwork into Schlemm's canal.[182-184]

Benefits of Combining Cataract Surgery and iStent Implantation

One of the key benefits of this study is that it was designed in part to examine the incremental benefits and risks of iStent combined with cataract surgery compared to those of cataract surgery alone. This study is the first randomized, controlled, multicenter trial of a glaucoma drainage device with cataract surgery vs cataract surgery alone. We can conclude that the iStent device provides the following benefits to patients undergoing cataract surgery:

1. IOP REDUCTION RESULTING FROM THE CREATION OF A BYPASS THROUGH THE PRIMARY PHYSIOLOGIC OUTFLOW PATHWAY

2. COMPARABLE OVERALL SAFETY PROFILE TO THAT OF CATARACT SURGERY ALONE, WHICH HAS A STRONG SAFETY PROFILE AND RESULTS IN A HIGH LEVEL OF PATIENT SATISFACTION

3. 100% COMPLIANCE BY DESIGN WHILE PROVIDING A SIGNIFICANT REDUCTION IN MEDICATION BURDEN

4. USES THE PRIMARY NATURAL OUTFLOW PATHWAY TO FACILITATE INCREASED AQUEOUS HUMOR OUTFLOW

5. CONJUNCTIVAL-SPARING, THUS PRESERVING OPTIONS FOR FUTURE, MORE INVASIVE, SURGICAL OPTIONS, IF NECESSARY

6. OPTIMIZES EFFICIENCY, SAFETY, AND COST BY COMBINING TWO SURGICAL PROCEDURES INTO A SINGLE OPERATIVE EVENT

When combined with cataract surgery in subjects with mild-to-moderate open-angle glaucoma, the iStent conferred a treatment effect that was both clinically and statistically superior to that of cataract surgery alone with regard to IOP reduction with less use of medications. The treatment difference at the one year follow-up visit was 18 percentage points on the primary efficacy endpoint of proportion of subjects with IOP ≤21 mm Hg without ocular hypotensive medications (68% vs 50%, P=.004).[175]

The ophthalmic community recognizes the primary endpoint in this trial of IOP ≤21 mm Hg without medications to be clinically meaningful.[165] An IOP of 21 mm Hg or less is generally considered to be the threshold of "normal" IOP.[166-167] Reducing IOP to ≤21 mm Hg without medication is commonly used endpoint in clinical trials evaluating surgical glaucoma devices and is a frequently utilized definition of surgical success in glaucoma practices.[168-173] Thus, achieving IOP of ≤21 mm Hg without medication is generally recognized as conferring an important clinical benefit. In fact, a responder analysis in which the patient has achieved a clinically meaningful target provides insight into the extent of the benefit in the patient population. Thus, use of the iStent in conjunction with phacoemulsification provided a clinically meaningful benefit of reducing IOP to ≤21 mm Hg without medication to a greater extent than with cataract surgery alone.

There was also an 18% treatment difference in favor of the iStent plus cataract group (66%

vs 48%, P=.003) on the secondary efficacy endpoint of reduction of IOP by 20% without ocular hypotensive medications. A 20% IOP reduction is considered by the American Academy of Ophthalmology to be a Level A recommendation which means that it is "most important" to the patient care process.[173]

The addition of medication following surgery occurred later in the iStent plus cataract surgery group than in the cataract surgery alone group. A higher proportion of the cataract surgery alone group were on medication at one week than the iStent plus cataract surgery group at one year. The analyses of medication use after surgery suggest that in a significant proportion of subjects undergoing cataract surgery, implantation of the iStent could delay or eliminate the reintroduction of topical hypotensive medication post-operatively.

In this study, there was no difference between the mean change in IOP from preoperative washout to the one year postoperative follow-up visit. This is not surprising because investigators managed ocular hypotensive medication use in order to maintain IOP at 21 mm Hg or below during the course of the study. What is important to note is that the reduction of IOP achieved in the iStent group occurred with significantly lower medication usage than in the cataract surgery alone group. Medication use in the iStent group was 15% at 12 months compared to 35% in the cataract only group. This difference was statistically significant and provides a meaningful benefit to patients.

Most patients newly diagnosed with open-angle glaucoma are prescribed ocular hypotensive medications as first-line therapy. This medication regimen typically continues for the rest of a patient's life. The successful management of a patient's glaucoma, in terms of slowing the disease progression, is dependent on the patient's ability to adhere to

the recommended medication regimen and to persist with the therapy. The challenges with both adherence and persistence have been documented in the literature, and are due to inability to properly instill the eyedrops, cost considerations, and a lack of awareness of the slow but gradual loss of vision. The problems with medication administration are of significant clinical concern in light of the need to reduce IOP in order to retard damage to the optic nerve and associated visual field loss. Therefore, reduction of medication burden would be of significant benefit to patients.

With the exception of adverse events specifically related to stent malposition or obstruction, adverse events in both the iStent and cataract only groups were representative of the elderly, post-cataract surgery population evaluated in this study. There were no serious or unanticipated safety concerns related to implantation of the iStent in conjunction with cataract surgery. Subjects undergoing cataract surgery do so with the objective of improvement in vision. In this study, ≥95% of subjects in both groups achieved this objective. The stent-related complications were less frequent and less severe than those complications commonly associated with current *ab externo* aqueous shunts and trabeculectomy, such as bleb leak, bleb-related infection, and hypotony.[83,132,176-182,185,186] There have been no reports of sight-threatening device-related complications associated with the iStent device in this trial or in the literature, other clinical studies or other countries including key European countries, Canada and Armenia where the stent is commercially available. The iStent is believed to be the smallest device ever to be implanted in the human body. Consquently, implantation of this device is less traumatic than what

is required with standard tubes or shunts which are up to several thousand times larger by mass. Because the iStent is implanted *ab interno* through the same incision required for cataract surgery, no incising of the conjunctiva or sclera is required. This results in less trauma to the eye and also preserves the option for future surgical procedures should additional IOP lowering be required.

In conclusion, implantation of the iStent in patients undergoing cataract surgery resulted in clinically and statistically significant benefits compared to cataract surgery alone. Furthermore, these benefits were achieved with a favorable safety profile. Thus, it can be concluded that in patients with mild to moderate open-angle glaucoma undergoing cataract surgery, the benefit of the iStent clearly exceeds the risk.

e) Two–Year Follow–Up

The consistent cohort at 24 months comprised successfully treated subjects, with preoperative, month 12, and month 24 data, and without surgical interventions that could confound IOP. This cohort included 98 eyes in the stent group and 101 eyes in the cataract only group.[187]

At 24 months, a significantly higher proportion of subjects (61%) implanted with a single iStent in conjunction with cataract surgery achieved the outcome of IOP ≤21 mm Hg without ocular hypotensive medications compared to 50% of subjects undergoing cataract surgery only (*P*=.036). The treatment effect for Month 24 IOP reduction ≥20% without medications showed a trend in favor of the stent group (53%, vs 44% in the control group; *P*=.09).

After medication washout and prior to surgery, mean IOP was 25.4 mm Hg (±3.6) in the stent group and 25.2 mm Hg (±3.6) in the cataract group. Mean IOP at 12 months postoperative

was 17.0 mm Hg (±2.8) in the stent group and 17.0 mm Hg (±3.1) in the control group, with subjects on an average of 0.2 (±0.6) medications in the stent group and 0.4 (±0.7) medications in the cataract group. The difference in Month 12 medication use was significant (P=.011). At 24 months, mean IOP in the stent group was essentially unchanged at 17.1 mm Hg (±2.9), with medication usage up only slightly to an average of 0.3 (±0.6) medications. Mean IOP in the cataract group increased to 17.8 mm Hg (±3.3), with subjects taking an average of 0.5 (±0.7) medications.

Adverse events occurred at low rates during the 24-month follow-up period and were typical of complications that occur in an older population undergoing cataract surgery. As in the first 12 months of follow-up, there were no serious or unanticipated device related adverse events reported between the 12 and 24 month follow-up visits. There were no significant changes in best corrected visual acuity between one and two years and visual field and pachymetry were also relatively stable over this period. Furthermore, none of the late-onset complications commonly reported with incisional glaucoma procedures such as bleb-related infections or hypotony were reported.

iSTENT SUSTAINS REDUCTIONS IN IOP AND MEDICATIONS[187]
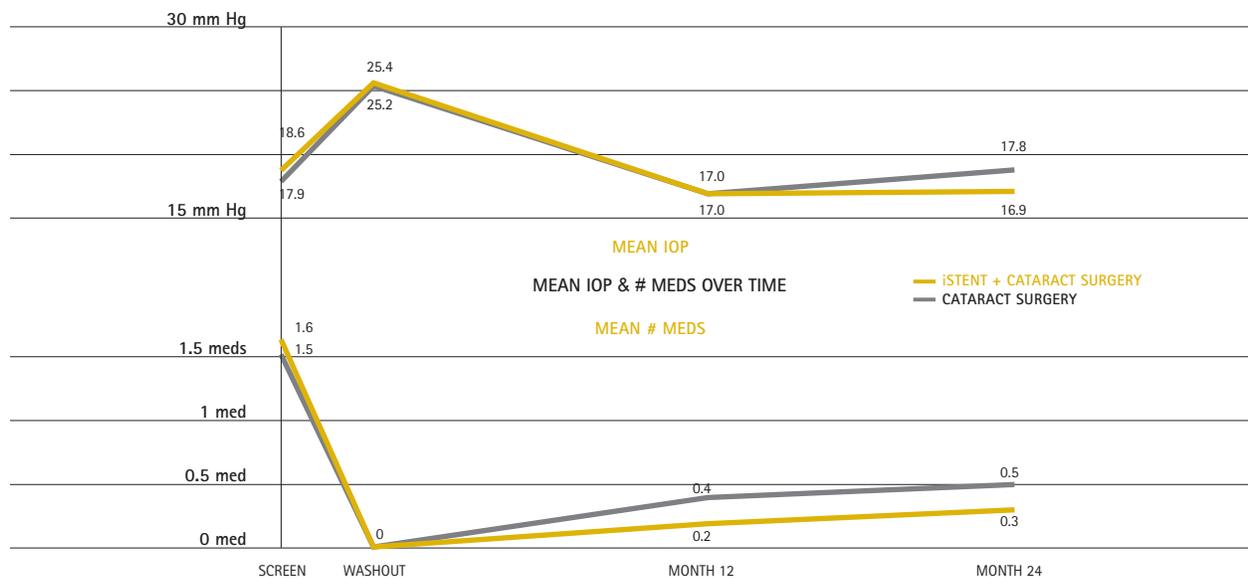
Figure 13. At 24 months, patients who received iStent achieved a 33% reduction in post-washout mean IOP and a 82% reduction in the mean number of medications.

2. TERMINAL WASHOUT TRIAL

The pivotal FDA trial did not have a terminal washout, and physicians were instructed to add medications when target IOP exceeded 21 mm Hg; thus, the pivotal trial was not designed to determine differences in mean IOP compared to cataract surgery. However, Fea conducted a prospective,

double-masked, randomized, controlled clinical trial that included a medication washout. In this trial, phacoemulsification alone (control) was compared to phacoemulsification and stent implantation (combined) in eyes with primary open-angle glaucoma. Enrollment consisted of 24 (21 completing and analyzed) patients in the control group and 12 in the combined group. Primary

outcomes included IOP and reduction in medication use through 15 months, and IOP after a 1-month washout. At baseline, both groups had similar mean IOPs (17.9 ± 2.6 mm Hg and 17.3 ± 3.0 mm Hg in the combined and control group, respectively, P=.512). Three patients in the control group were lost to follow-up: One had a capsule rupture, 1 did not present, and 1 died (not related to the cataract surgery). Mean IOP was lower in the combined group than in the control group at 15 months (14.8 ± 1.2 mm Hg vs 15.7 ± 1.1 mm Hg, respectively, P=.031) and after the washout (16.6 ± 3.1 mm Hg vs 19.2 ± 3.5 mm Hg respectively, P=.042). The mean number of medications was also lower in the combined group than the control group

at 15 months (0.4 ± 0.7 vs 1.3 ± 1.0 medications, respectively, P=.007), as were the proportion of patients using ocular hypotensive medications, (33% [4/12] and 76% [16/21], respectively). Based on IOP change postwashout vs baseline, iStent plus cataract surgery resulted in an IOP reduction 3.2 mm Hg greater than that of cataract surgery alone. Results from the Early Manifest Glaucoma Trial indicated that risk of glaucomatous progression decreased by approximately 10% with each 1 mm Hg reduction in IOP from baseline.[34] Thus, the incremental IOP-lowering effect of iStent implantation over cataract surgery alone confers a substantial clinical improvement in this population.

IN A SEPARATE CLINICAL TRIAL[188]
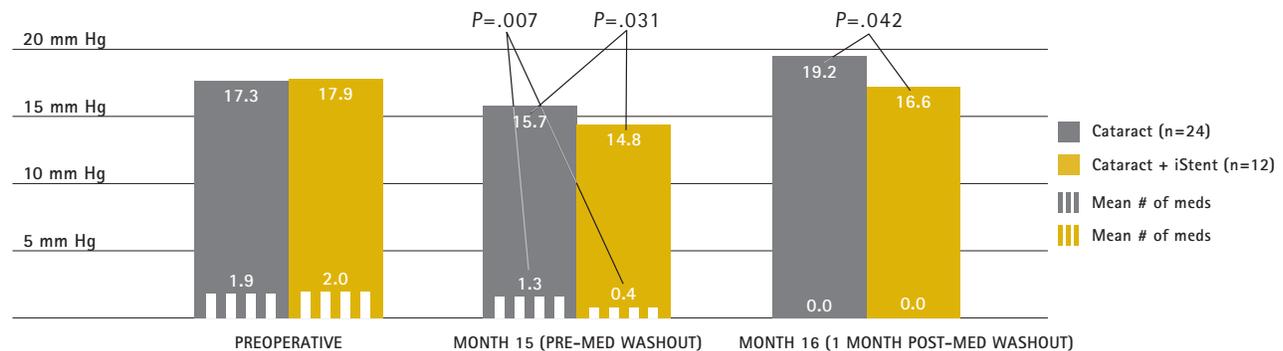
An additional 3 mm Hg reduction in IOP is the mean reduction commonly associated with adjunctive glaucoma medications.

Figure 14. In a prospective, randomized, double-masked study, 67% of patients who received iStent remained medication-free at 15 months vs only 24% of patients who underwent cataract surgery alone (P=.027).

3. PROSPECTIVE CASE SERIES

A prospective, single-arm, multicenter study enrolled 58 patients who underwent clear cornea phacoemulsification followed by *ab interno* gonioscopically guided implantation of iStent. Data through 12 months on 42 of the 48 per-protocol patients are summarized.[184]

At baseline, IOP was 21.7 mm Hg ± 3.9 mm Hg on a mean 1.6 ± 0.8 medications. By 12 months, the mean number of medications was reduced to 0.4 ± 0.62 (P<.001). At 12 months, mean IOP was reduced to 17.4 ± 2.99 mm Hg, a reduction of 4.4 ± 4.54 mm Hg (18.3%, P<.001). By the 12

month visit, one-half of the patients were no longer on medication with an IOP <18 mm Hg.

Stent obstruction and malposition were the most commonly reported complications (12% and 10%, respectively). There were no serious adverse events.

F. COST-EFFECTIVENESS

As mentioned previously, the American Academy of Ophthalmology (AAO) states the following in its "Preferred Practice Pattern for Primary Open-Angle Glaucoma":

Patients with primary open-angle glaucoma who have a visually significant cataract have a range of options to consider. If IOP control is at target on one or few medications, cataract surgery alone may be adequate, with the additional benefit that it may lower IOP slightly....Cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2 mm Hg on average.

The pivotal clinical trial for the iStent Trabecular Micro-Bypass Stent represents the first IDE trial using a multicenter, prospective, randomized trial design for a glaucoma device. The results of the clinical trial clearly demonstrate that in the cataract plus mild to moderate open-angle glaucoma population, iStent results in clinically significant positive outcomes.

Any cost-effectiveness analysis of a glaucoma surgical device such as the iStent Trabecular Micro-Bypass Stent should address:

1. NET IMPROVEMENT IN PATIENT (VISUAL) OUTCOMES AND QUALITY OF LIFE

2. REDUCTIONS IN MEDICATION USE

3. ASSOCIATED MANAGEMENT COSTS (DIAGNOSTIC TESTING, OFFICE VISITS) RELATED TO ONGOING MANAGEMENT AND THERAPY CHANGES

4. USE OF SURGICAL INTERVENTIONS WITH COSTS ADJUSTED FOR COMPLICATIONS AND ADVERSE EVENTS

At this time, a formal cost-effectiveness analysis of the iStent Trabecular Micro-Bypass Stent has not been completed given the limited duration of follow-up data. However, we will be developing such models once longer-term outcomes data become available. In the mean time, there are a number of factors indicating that implantation of the iStent device in conjunction with cataract surgery in mild to moderate open-angle glaucoma patients is a cost-effective intervention for this population in light of the high cost per beneficiary for managing open-angle glaucoma.

1. BURDEN OF GLAUCOMA TREATMENT AND ANNUAL COST PER MEDICARE PATIENT

It was estimated that the treatment of glaucoma cost the US health care system $2.9 billion in 2008.[189] Open-angle glaucoma is a chronic disease with no cure, and treatment of the disease incurs substantial annual costs that tend to increase over time as the disease progresses. In a retrospective study involving 151 records at 12 sites in the United States, the annual average direct cost of treatment was found to be $1581, with average annual costs ranging from $615 for patients in the earliest stage of the disease to $2203 for patients in the latest stage of the disease.[9]

We also explored the issue of the costs of glaucoma management specifically in a Medicare population undergoing cataract surgery. An analysis of the Medicare Standard Analytical file for 2002 to 2007 was conducted.[147] Specifically, this analysis found that glaucoma-related costs among beneficiaries with a diagnosis of open-angle glaucoma for the 4-year period following cataract surgery averaged $1895 per year.

Given that old age is a confirmed risk factor for glaucoma and that the prevalence of glaucoma is 5 to 10 times higher among 75-year-olds versus 40-year-olds, the cost of treating glaucoma in the United States falls disproportionately on the Medicare program.

2. COST EFFICIENCIES DUE TO COMBINATION WITH CATARACT SURGERY

Combining implantation of the iStent with cataract surgery results in significant cost efficiencies versus other glaucoma surgeries involving implantable devices, as the latter are generally implanted in stand-alone procedures. The incremental facility payment at the national Medicare rate for implantation of the iStent in the HOPD site of service over and above the payment for cataract surgery is $2075.09. This

compares to $2911.11 for implantation of an *ab externo* aqueous shunt (CPT codes 66180 and 0192T) in a stand-alone procedure, representing a savings of greater than $836.

3. COST EFFICIENCIES DUE TO SITE OF SERVICE

The vast majority of cataract surgeries performed in the United States are performed in the ASC site of service, while the majority of aqueous shunt implantation surgeries are performed in the HOPD site of service. This will result in additional cost savings, as the incremental facility payment for implantation of the iStent over that for cataract surgery in the ASC site of service is $1195.88. This represents a savings of greater than $1715 versus implantation of an aqueous shunt in the HOPD site of service in a stand-alone procedure.

4. SECONDARY SURGICAL INTERVENTIONS

The results of the pivotal trial indicate that implantation of the iStent device significantly lowers IOP versus baseline. Numerous studies have indicated that reduction of IOP slows disease progression and thus the need for additional interventions.[33-35,81] Results from the pivotal trial also indicate that no subjects in the iStent group required incisional surgery for control of IOP and only 1 subject required laser trabeculoplasty.

5. COST OF MANAGING COMPLICATIONS

The results of the pivotal trial also indicated that overall complication rates were similar between iStent in conjunction with cataract surgery and cataract surgery alone. Thus, it would be expected that incremental costs associated with post-op management of patients implanted with the iStent in conjunction with cataract surgery versus patients undergoing cataract surgery alone would be modest. This compares very favorably to the cost of managing complications following implantation of an *ab externo* aqueous shunt. In a separate analysis of the 2002 to 2007 Medicare Statistical Analytical file[147] among subjects undergoing aqueous shunt implantation (CPT code 66180), the cost of treating complications associated with the surgery over the next 4 years averaged $3091 per beneficiary.

6. MEDICATION REDUCTION

In the pivotal trial, subjects who received the iStent device in conjunction with cataract surgery experienced a mean decrease in medication usage of 1.3 medications from the screening visit to the 1-year follow-up visit.

G. SUMMARY

iStent provides a sustainable foundation in reestablishing physiologic outflow, achieving target pressures, and reducing or eliminating the need for ocular hypotensive medications.

A single iStent implanted in conjunction with cataract surgery:

1. IMPROVES AQUEOUS OUTFLOW THROUGH THE NATURAL PHYSIOLOGIC OUTFLOW PATHWAY

2. REDUCES IOP

3. SPARES THE CONJUNCTIVA

4. HAS AN OVERALL SAFETY PROFILE SIMILAR TO THAT OF CATARACT SURGERY ALONE

5. SAFELY PRESERVES PATIENT CANDIDACY FOR FUTURE TREATMENT OPTIONS

iStent is the only currently available FDA-approved device for the treatment of mild-to-moderate open-angle glaucoma in combination with cataract surgery.

The iStent Trabecular Micro-Bypass Stent is a "first in class" device that improves aqueous outflow through the natural physiologic

pathway. The iStent addresses an important gap in the current treatment algorithm, which specifically addresses mild-to-moderate open-angle glaucoma patients. The results of the pivotal IDE study clearly indicate that implantation of the iStent device provides a substantial clinical improvement for adult patients diagnosed with mild-to-moderate open-angle glaucoma undergoing cataract surgery. In addition, the iStent device represents a much needed alternative to devices currently available for the treatment of open-angle glaucoma (ie, *ab externo* aqueous shunts).

INDICATION FOR USE

The iStent® Trabecular Micro-Bypass Stent (Models GTS100R and GTS100L) is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

CONTRAINDICATIONS

The iStent® is contraindicated in eyes with primary or secondary angle closure glaucoma, including neovascular glaucoma, as well as in patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure.

WARNINGS

Gonioscopy should be performed prior to surgery to exclude PAS, rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. The iStent® is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions, please see label for details.

PRECAUTIONS

The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The safety and effectiveness of the iStent® has not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, chronic inflammation, or an abnormal anterior segment, in pseudophakic patients with glaucoma, in patients with pseudoexfoliative glaucoma, pigmentary, and uveitic glaucoma, in patients with unmedicated IOP less than 22 mmHg or greater than 36 mmHg after "washout" of medications, or in patients with prior glaucoma surgery of any type including argon laser trabeculoplasty, for implantation of more than a single stent, after complications during cataract surgery, and when implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract.

ADVERSE EVENTS

The most common post-operative adverse events reported in the randomized pivotal trial included early post-operative corneal edema (8%), BCVA loss of ≥ 1 line at or after the 3 month visit (7%), posterior capsular opacification (6%), stent obstruction (4%) early post-operative anterior chamber cells (3%), and early post-operative corneal abrasion (3%). Please refer to Directions for Use for additional adverse event information.

CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please reference the Directions for Use labeling for a complete list of contraindications, warnings, precautions, and adverse events.

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The US Food and Drug Administration (FDA) has approved the iStent® Trabecular Micro-Bypass Stent System for commercial use when used in accordance with the indications for use.

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